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(54) Title: INDANE, DIHYDROBENZOFURAN, AND TETRAHYDRONAPHTHALENE CARBOXYLIC ACID DERIVATIVES AND THEIR USE AS ANTIDIABETICS

(57) Abstract: This invention relates to novel indane, dihydrobenzofuran, and tetrahydronaphthalene carboxylic acid derivatives whice are useful in the treatment of diseases such sa diabetes, diabetes-related disorders, obesity, hyperlipidemia, and cardiovascular diseases. The invention also relates to intermediates useful in preparation of said carboxylic derivatives and to methods of preparation.

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INDANE, DIHYDROBENZOFURAN, AND TETRAHYDRONAPHTHALENE CARBOXYLIC ACID DERIVATIVES AND THEIR USE AS ANTIDIABETICS

[001] This application claims benefit of U.S. Provisional Application Serial No. 60/399,095, filed July 26, 2002, the contents of which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

[002] This invention is directed to the use of indane, dihydrobenzofuran, and tetrahydronaphthalene carboxylic acid derivatives and pharmaceutical compositions useful in the treatment of diseases such as diabetes, obesity, hyperlipidemia, and atherosclerotic disease. The invention is also directed to intermediates useful in preparation of said carboxylic derivatives and to methods of preparation.

BACKGROUND OF THE INVENTION

[003] Non-insulin-dependent diabetes mellitus (NIDDM), or type 2 diabetes, is the more common form of diabetes, with 90-95% of hyperglycemic patients experiencing this form of the disease. In NIDDM, there appears to be a reduction in the pancreatic β-cell mass, several distinct defects in insulin secretion, or a decrease in tissue sensitivity to insulin. The symptoms of this form of diabetes include fatigue, frequent urination, thirst, blurred vision, frequent infections and slow healing of sores, diabetic nerve damage, retinopathy, and renal disease.

[004] Resistance to the metabolic actions of insulin is one of the key features of non-insulin dependent diabetes. Insulin resistance is characterized by impaired uptake and utilization of glucose in insulin-sensitive target organs, for example, adipocytes and skeletal muscle, and by impaired inhibition of hepatic glucose output. The functional insulin deficiency and the failure of insulin to suppress hepatic glucose output results in fasting hyperglycemia. Pancreatic β-cells compensate for the insulin resistance by secreting increased levels of insulin. However, the β-cells are unable to maintain this high output of insulin, and eventually, the glucose-induced insulin secretion falls, leading to the deterioration of glucose homeostasis and to the subsequent development of overt diabetes. Hyperinsulinemia is also linked to insulin resistance, hypertriglyceridemia, and increased plasma concentration of low-density lipoproteins. The association of insulin resistance and hyperinsulinemia with these metabolic disorders has been termed

"Syndrome X" and has been strongly linked to an increased risk of hypertension and coronary artery disease.

[005] Obesity is an excessive accumulation of adipose tissue. Excess adipose tissue is associated with the development of serious medical conditions, for example, NIDDM, hypertension, coronary artery disease, hyperlipidemia, obesity, and certain malignancies. The adipocyte may also influence glucose homeostasis through the production of tumor necrosis factor α (TNFα) and other molecules.

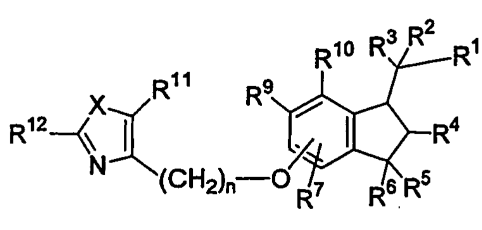
[006] Atherosclerotic disease is known to be caused by a number of factors, for example, hypertension, diabetes, low levels of high-density lipoprotein (HDL), and high levels of low-density lipoprotein (LDL). Atherosclerotic diseases include cardiovascular disease, coronary heart disease (CHD), cerebrovascular disease, and peripheral vessel disease. Coronary heart disease includes CHD death, myocardial infarction, and coronary revascularization. Cerebrovascular disease includes ischemic or hemorrhagic stroke, and transient ischemic attacks.

[007] Accordingly, despite the presence of some pharmaceuticals that are used to treat these diseases, there remains a need for new pharmaceuticals that are both safe and effective agents for the treatment of disease, and for useful methods to prepare them.

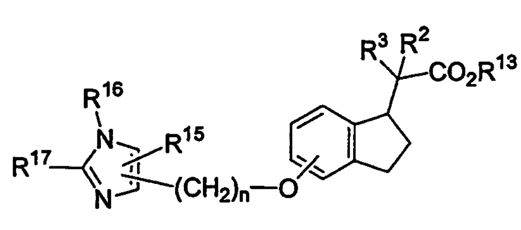
[008] The present invention relates to compounds which are useful in the treatment of diabetes and related disorders such as Syndrome X, impaired glucose tolerance, impaired fasting glucose, and hyperinsulinemia; obesity; atherosclerotic disease and related disorders such as hypertriglyceridemia and hypercholesteremia; cardiovascular disease, and cerebrovascular disease.

DESCRIPTION OF THE INVENTION

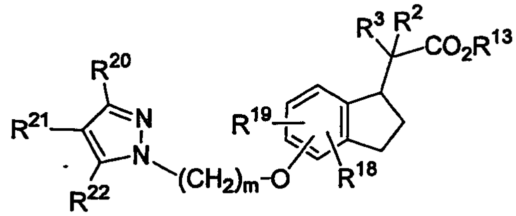
[009] The present invention encompasses the compounds of Formulae (Ia)-(Ie),



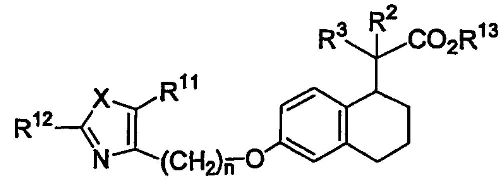
(Ia)



(Ib)



(Ic)



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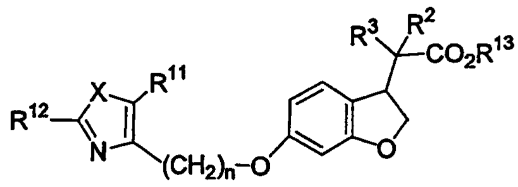


(Ie)

wherein

X is O or S;

n is 1, 2, or 3;

m is 2 or 3;

R^1 is CO_2H, $CO_2(C_1\text{-}C_6)$alkyl, C(=O)NH-CN, $CH_2NR^8R^8$, $C(=O)NR^8R^8$,

wherein each R^8 is independently selected from H and $(C_1\text{-}C_6)$alkyl;

R^2 is H, F, or $(C_1\text{-}C_6)$alkyl;

R^3 is H, F, or $(C_1\text{-}C_6)$alkyl;

R^4 is H or $(C_1\text{-}C_6)$alkyl;

R^5 is H or $(C_1\text{-}C_6)$alkyl;

R^6 is H or $(C_1\text{-}C_6)$alkyl;

R^7 is H, $(C_1\text{-}C_6)$alkoxy, OH, O-SO_2CF_3, halo, 1,3-benzodioxolyl, or phenyl optionally substituted with one or more $(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$alkoxy;

R^9 is H, Br, Cl, I, $(C_1\text{-}C_6)$alkyl, $(CH_2)_2$-phenyl, -CH=CH-phenyl, -C≡C-phenyl, allyl;

R^{10} is H, O-SO_2CF_3, 1,3-benzodioxolyl, or phenyl,

wherein said phenyl is optionally substituted with one or more $(C_1\text{-}C_6)$alkyl, halo, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkylthio, or CF_3;

R^{11} is H, $(C_1\text{-}C_3)$alkyl, or -CH_2CH_2-phenyl,

wherein said phenyl is optionally substituted with one or more $(C_1\text{-}C_6)$alkoxy, halo, or $(C_1\text{-}C_6)$alkyl;

R^{12} is selected from

naphthyl,

pyridyl optionally substituted with phenyl optionally substituted with halo,

(C_1-C_3)alkyl, or (C_1-C_3)alkoxy, and

phenyl optionally substituted with

one or more halo,

NH_2,

benzylamino,

one or more (C_1-C_4)alkyl,

(C_2-C_4)alkenyl,

pyrrolyl,

1,3-benzodioxolyl,

NO_2,

CF_3,

(C_1-C_3)alkylthio,

one or more (C_1-C_3)alkoxy,

phenyl optionally substituted with halo, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy,

isoxazolyl optionally substituted by CH_3 or (C_1-C_3)alkyl, or

pyrimidyl optionally substituted by OH,

and in the case where X is S, R^{12} is additionally selected from NHR^{14},

wherein

R^{14} is H,

C(=O)NH-phenyl,

wherein said phenyl is optionally substituted with one or more NH_2, NO_2, (C_1-C_4)alkyl, halo, or (C_1-C_6)alkoxy,

SO_2-phenyl,

wherein said phenyl is optionally substituted with one or more NH_2, (C_1-C_4)alkyl, NO_2, halo, or (C_1-C_6)alkoxy,

SO_2-(C_1-C_4)alkyl,

C(=O)-O-(C_1-C_4)alkyl,

C(=O)-(C_1-C_4)alkyl,

C(=O)-(C_3-C_6)cycloalkyl,

C(=O)-naphthyl, or

C(=O)-phenyl,

wherein said phenyl is optionally substituted with one or more (C_1-C_4)alkyl, halo, (C_1-C_4)alkoxy, NO_2, NH_2, or phenyl optionally substituted with one or more (C_1-C_4)alkyl, halo, (C_1-C_4)alkoxy, NO_2, or NH_2;

R^{13} is H or $(C_1\text{-}C_6)$alkyl;

R^{15} is H or $(C_1\text{-}C_3)$alkyl;

R^{16} is H or $(C_1\text{-}C_6)$alkyl optionally substituted with phenyl,

wherein said phenyl is optionally substituted with one or more halo, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or NO_2;

R^{17} is 1,3-benzodioxolyl,

naphthyl,

pyridyl optionally substituted with phenyl optionally substituted with halo, $(C_1\text{-}C_3)$alkyl, or $(C_1\text{-}C_3)$alkoxy, or

phenyl optionally substituted with one or more of the following

halo,

NH_2,

benzylamino,

$(C_1\text{-}C_4)$alkyl,

$(C_2\text{-}C_4)$alkenyl,

pyrrolyl,

1,3-benzodioxolyl,

NO_2,

CF_3,

$(C_1\text{-}C_3)$alkylthio,

$(C_1\text{-}C_3)$alkoxy,

pyridyl,

phenyl optionally substituted with halo, $(C_1\text{-}C_3)$alkyl, or $(C_1\text{-}C_3)$alkoxy,

isoxazolyl optionally substituted with CH_3 or $(C_1\text{-}C_3)$alkyl, or

pyrimidyl optionally substituted with OH;

R^{18} is H or F;

R^{19} is H, Cl, or Br;

R^{20} is $(C_1\text{-}C_6)$alkyl or phenyl optionally substituted by CO_2H, $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_6)$alkoxy, or CF_3;

R^{21} is H, halo, $(C_1\text{-}C_6)$alkyl, 1,3-benzodioxolyl, phenyl,

wherein said phenyl is optionally substituted with one or more CO_2H, halo, $(C_1\text{-}C_6)$alkyl, CF_3, or $(C_1\text{-}C_6)$alkoxy;

R^{22} is $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_3)$alkyl, or CF_3;

and pharmaceutically salts and esters thereof;

provided that in Formula (Ia), at least one of the following is true

- n is 1 or 3;
- R^1 is C(=O)NH-CN, $CH_2NR^8R^8$, or C(=O)NR^8R^8;
- one of R^2 or R^3 is F;
- both R^2 and R^3 are (C_1-C_6)alkyl;
- R^4 is (C_1-C_6)alkyl;
- one of R^5 or R^6 is (C_1-C_6)alkyl;
- R^{10} is O-SO_2CF_3, 1,3-benzodioxolyl, or phenyl optionally substituted with one or more (C_1-C_6)alkyl, halo, (C_1-C_6)alkoxy, (C_1-C_6)alkylthio, or CF_3;
- R^{11} is -CH_2CH_2-phenyl,
  wherein said phenyl is optionally substituted with one or more (C_1-C_6)alkoxy, halo, or (C_1-C_6)alkyl;
- R^7 is attached at the 5 position of the indane ring;

or

- R^{12} is NHR^{14} and X = S.

[010] In Formula (Ia), R^7 is attached to the dihydroindene ring at either the 4 or the 5 position, and the oxazole-alkoxy group (when X = O) or thiazole-alkoxy group (when X = S) is attached to the dihydroindene ring at either the 4 or the 5 position, such that the R^7 group and oxazole-alkoxy or thiazole-alkoxy groups are located on non-identical positions of the dihydroindene ring.

[011] In Formula (Ib), the O atom of the –$(CH_2)_n$-O- linker is attached at either the 4 or the 5 position of the dihydroindene ring, the C atom of the –$(CH_2)_n$-O- linker is attached at either the 4 or the 5 position of the imidazole ring, and the R^{15} group is attached at either the 4 or 5 position of the imidazole ring, such that the R^{15} group and the -$(CH_2)_n$-O- linker are located on non-identical positions of the imidazole ring.

[012] In Formula (Ic), R^{19} is attached to the dihydroindene ring at either the 5 or 6 carbon, R^{18} is attached to the dihydroindene ring at either the 4 or 5 position, and the pyrazole-alkoxy group is attached at either the 4 or the 5 position of the dihydroindene ring, so long as the positions of the R^{18} group, R^{19} group, and pyrazole-alkoxy groups are not identical.

[013] The terms identified above have the following meaning throughout:

[014] The term "optionally substituted" means that the moiety so modified may have from none to up to at least the highest number of substituents possible. The substituent may replace any H atom on the moiety so modified as long as the replacement is chemically possible and chemically stable. When there are two or more substituents on any moiety, each substituent is chosen independently of any other substituent and can, accordingly, be the same or different.

[015] The term "halo" means an atom selected from Cl, Br, F, and I.

[016] The terms "(C_1-C_3)alkyl," "(C_1-C_4)alkyl," and "(C_1-C_6)alkyl" mean linear or branched saturated carbon groups having from about 1 to about 3, about 4, or about 6 C atoms, respectively. Such groups include, but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, and the like.

[017] The term "(C_2-C_4)alkenyl" means a linear or branched unsaturated carbon group having from about 2 to about 4 C atoms in which a double bond is present between any two available carbons in the group and includes such groups as 1-ethenyl, 2-propenyl, isopropenyl, 2-methyl-2-propenyl, 2-butenyl, 3-butenyl, and the like.

[018] The term "(C_3-C_6)cycloalkyl" means a saturated monocyclic alkyl group of from about 3 to about 6 carbon atoms and includes such groups as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

[019] The terms "(C_1-C_3)alkoxy," "(C_1-C_4)alkoxy," and "(C_1-C_6)alkoxy" mean a linear or branched saturated carbon group having from about 1 to about 3, about 4, or about 6 C atoms, respectively, said carbon group being attached to an O atom. The O atom is the point of attachment of the alkoxy substituent to the rest of the molecule. Such groups include, but are not limited to, methoxy, ethoxy, *n*-propoxy, isopropoxy, and the like.

[020] The term "(C_1-C_3)alkylthio" and "(C_1-C_6)alkylthio" means a linear or branched saturated carbon group having from about 1 to about 3 C atoms or about 6 C atoms, said carbon group being attached to an S atom. The S atom is the point of attachment of the alkylthio substituent to the rest of the molecule. Such groups, include but are not limited to, methylthio, ethylthio, *n*-propylthio, isopropylthio, and the like.

[021] When "(=O)" is used in a chemical formula, it means =O, that is, an O that is double bonded to the C atom to which it is attached.

[022] When a phenyl ring or a heterocycle is attached to the rest of the molecule, it is attached by replacing any H atom on the phenyl ring or on the heterocycle, respectively, with a bond to the rest of the molecule.

[023] When a phenyl ring is substituted with one or more substituents, the substituent(s) may be attached to the phenyl ring at any available C atom. When there is more than one substituent on a phenyl ring, each substituent is selected independently from the other so that they may be the same or different.

[024] A salt of a compound of Formulae (Ia)-(Ie) may be prepared in situ during the final isolation and purification of a compound or by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Likewise, when the compound of Formulae (Ia)-(Ie) contains a carboxylic acid moiety, (e.g., R = H), a salt of said compound of Formulae (Ia)-(Ie) may be prepared by separately reacting it with a suitable inorganic or organic base and isolating the salt thus formed. The term "pharmaceutically acceptable salt" refers to a relatively non-toxic, inorganic or organic acid addition salt of a compound of the present invention (*see, e.g.*, Berge et al., J. Pharm. Sci. 66:1-19, 1977).

[025] Representative salts of the compounds of Formulae (Ia)-(Ie) include the conventional non-toxic salts and the quaternary ammonium salts which are formed, for example, from inorganic or organic acids or bases by means well known in the art. For example, such acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cinnamate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, itaconate, lactate, maleate, mandelate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, sulfonate, tartrate, thiocyanate, tosylate, undecanoate, and the like.

[026] Base salts include, for example, alkali metal salts such as potassium and sodium salts, alkaline earth metal salts such as calcium and magnesium salts, and ammonium salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine. Additionally, basic nitrogen containing groups in the conjugate base may be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, and dibutyl sulfate; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and streary chlorides, bromides and iodides; aralkyl halides like benzyl and phenethyl bromides, and the like.

[027] The esters of Formulae (Ia)-(Ie) in the present invention are non-toxic, pharmaceutically acceptable esters, for example, alkyl esters such as methyl, ethyl,

propyl, isopropyl, butyl, isobutyl, or pentyl esters. Additional esters such as, for example, methyl ester or phenyl-C_1-C_5 alkyl may be used. The compound of Formulae (Ia)-(Ie) may be esterified by a variety of conventional procedures including reacting the appropriate anhydride, carboxylic acid, or acid chloride with the alcohol group of the Formulae (Ia)-(Ie) compound. The appropriate anhydride may be reacted with the alcohol in the presence of a base to facilitate acylation such as 1,8-bis[dimethylamino]naphthalene or N,N-dimethylaminopyridine. An appropriate carboxylic acid may be reacted with the alcohol in the presence of a dehydrating agent such as dicyclohexylcarbodiimide, 1-[3-dimethylaminopropyl]-3-ethylcarbodiimide, or other water soluble dehydrating agents which are used to drive the reaction by the removal of water, and optionally, an acylation catalyst. Esterification may also be effected using the appropriate carboxylic acid in the presence of trifluoroacetic anhydride and optionally, pyridine, or in the presence of N,N-carbonyldiimidazole with pyridine. Reaction of an acid chloride with the alcohol may be carried out with an acylation catalyst such as 4-DMAP or pyridine.

[028] One skilled in the art would readily know how to successfully carry out these as well as other methods of esterification of alcohols.

[029] Additionally, sensitive or reactive groups on the compound of Formulae (Ia)-(Ie) may need to be protected and deprotected during any of the above methods for forming esters. Protecting groups in general may be added and removed by conventional methods well known in the art (*see, e.g.*, T. W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis;* Wiley: New York, 1999).

[030] The compounds of Formulae (Ia)-(Ie) may contain one or more asymmetric centers, depending upon the location and nature of the various substituents desired. Asymmetric carbon atoms may be present in the (*R*) or (*S*) configuration. Preferred isomers are those with the absolute configuration which produces the compound of Formulae (Ia)-(Ie) with the more desirable biological activity. In certain instances, asymmetry may also be present due to restricted rotation about a given bond, for example, the central bond adjoining two aromatic rings of the specified compounds.

[031] Substituents on a ring may also be present in either cis or trans form, and a substituent on a double bond may be present in either *Z* or *E* form.

[032] It is intended that all isomers (including enantiomers and diastereomers), either by nature of asymmetric centers or by restricted rotation as described above, as separated, pure or partially purified isomers or racemic mixtures thereof, be included within the

scope of the instant invention. The purification of said isomers and the separation of said isomeric mixtures may be accomplished by standard techniques known in the art.

[033] The particular process to be utilized in the preparation of the compounds of this invention depends upon the specific compound desired. Such factors as the selection of the specific X moiety, and the specific substituents possible at various locations on the molecule, all play a role in the path to be followed in the preparation of the specific compounds of this invention. Those factors are readily recognized by one of ordinary skill in the art.

[034] Compounds of the present invention may be made according to the following General Reaction Schemes 1-29. In these schemes, unless otherwise noted, R^1-R^{22}, X, n, and m have the same definitions as described above. The following specific examples are presented to illustrate the invention described herein, but they should not be construed as limiting the scope of the invention in any way.

Preparation of Compounds of the Inventions

General Experimental Methods

[035] In general, the compounds used in this invention may be prepared by standard techniques known in the art, by known processes analogous thereto, and/or by the processes described herein, using starting materials which are either commercially available or producible according to routine, conventional chemical methods. The following preparative methods are presented to aid the reader in the synthesis of the compounds of the present invention.

[036] Air and moisture sensitive liquids and solutions were transferred via syringe or cannula, and introduced into reaction vessels through rubber septa. Commercial grade reagents and solvents were used without further purification. The term "concentration under reduced pressure" or "*in vacuo*" refers to use of a Buchi rotary evaporator at approximately 15 mm of Hg. All temperatures are reported uncorrected in degrees Celsius (°C).

[037] Thin layer chromatography (TLC) was performed on EM Science pre-coated glass-backed silica gel 60 A F-254 250 μm plates. Column chromatography (flash chromatography) was performed on a Biotage system using 32-63 micron, 60 A, silica gel pre-packed cartridges. Purification using preparative reversed-phase HPLC chromatography were accomplished using a Gilson 215 system, using a YMC Pro-C18 AS-342 (150 x 20 mm I.D.) column. Typically, the mobile phase used was a mixture of H_2O (A) and MeCN (B). The water may be mixed with 0.1% TFA. A typical gradient is described below:

Time [min]	A: %	B: %	Flow [mL/min]
0.50	90.0	10.0	1.0
11.00	0.0	100.0	1.0
14.00	0.0	100.0	1.0
15.02	100.0	0.0	1.0

[038] Chiral analytical HPLC experiments were performed using one of the two following methods using a Varian Pro Star 1200:

A: Column: Chiracel AD, 4.6 (I.D.) x 250 mm
Mobile Phase: A: 0.1% TFA in hexanes; B: 0.1% TFA in *i*-PrOH; Isocratic: 95%A (5%B), 20 min.

Flow Rate: 1.5 mL/min

Detector (UV): 284 nm

B: Column: Chiracel AD, 4.6 (I.D.) x 250 mm

Mobile Phase: A: 0.1% TFA in hexanes; B: 0.1% TFA in *i*-PrOH

Isocratic: 95%A (5%B), 25 min.

Flow Rate: 1.0 mL/min

Detector (UV): 284 nm

[039] Electron impact mass spectra (EI-MS or GC-MS) were obtained with a Hewlett Packard 5989A mass spectrometer equipped with a Hewlett Packard 5890 Gas Chromatograph with a J & W DB-5 column (0.25 uM coating; 30 m x 0.25 mm). The ion source was maintained at 250°C and spectra were scanned from 50-800 amu at 2 sec per scan. High pressure liquid chromatography-electrospray mass spectra (LC-MS) were obtained using a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector set at 254 nm, a YMC pro C-18 column (2 x 23 mm, 120A), and a Finnigan LCQ ion trap mass spectrometer with electrospray ionization. Spectra were scanned from 120-1200 amu using a variable ion time according to the number of ions in the source. The eluents were A: 2% acetonitrile in water with 0.02% TFA and B: 2% water in acetonitrile with 0.018% TFA. Gradient elution from 10% B to 95% over 3.5 minutes at a flowrate of 1.0 mL/min was used with an initial hold of 0.5 minutes and a final hold at 95% B of 0.5 minutes. Total run time was 6.5 minutes. For consistency in characterization data, the retention time (RT) is reported in minutes at the apex of the peak as detected by the UV-Vis detector set at 254 nm.

[040] Routine one-dimensional NMR spectroscopy was performed on 300 or 400 MHz Varian Mercury-plus spectrometers. The samples were dissolved in deuterated solvents obtained from Cambridge Isotope Labs, and transferred to 5mm ID Wilmad NMR tubes. The spectra were acquired at 293 K. The chemical shifts were recorded on the ppm scale and were referenced to the appropriate residual solvent signals, such as 2.49 ppm for DMSO-*d6*, 1.93 ppm for CD_3CN, 3.30 ppm for CD_3OD, 5.32 ppm for CD_2Cl_2, and 7.26 ppm for $CDCl_3$ for ^1H spectra, and 39.5 ppm for DMSO-*d6*, 1.3 ppm for CD_3CN, 49.0 ppm for CD_3OD, 53.8 ppm for CD_2Cl_2, and 77.0 ppm for $CDCl_3$ for ^{13}C spectra.

[042] General methods of preparation are illustrated in the reaction schemes, and by the specific preparative examples that follow.

ABBREVIATIONS AND ACRONYMS

[043] When the following abbreviations are used herein, they have the following meaning:

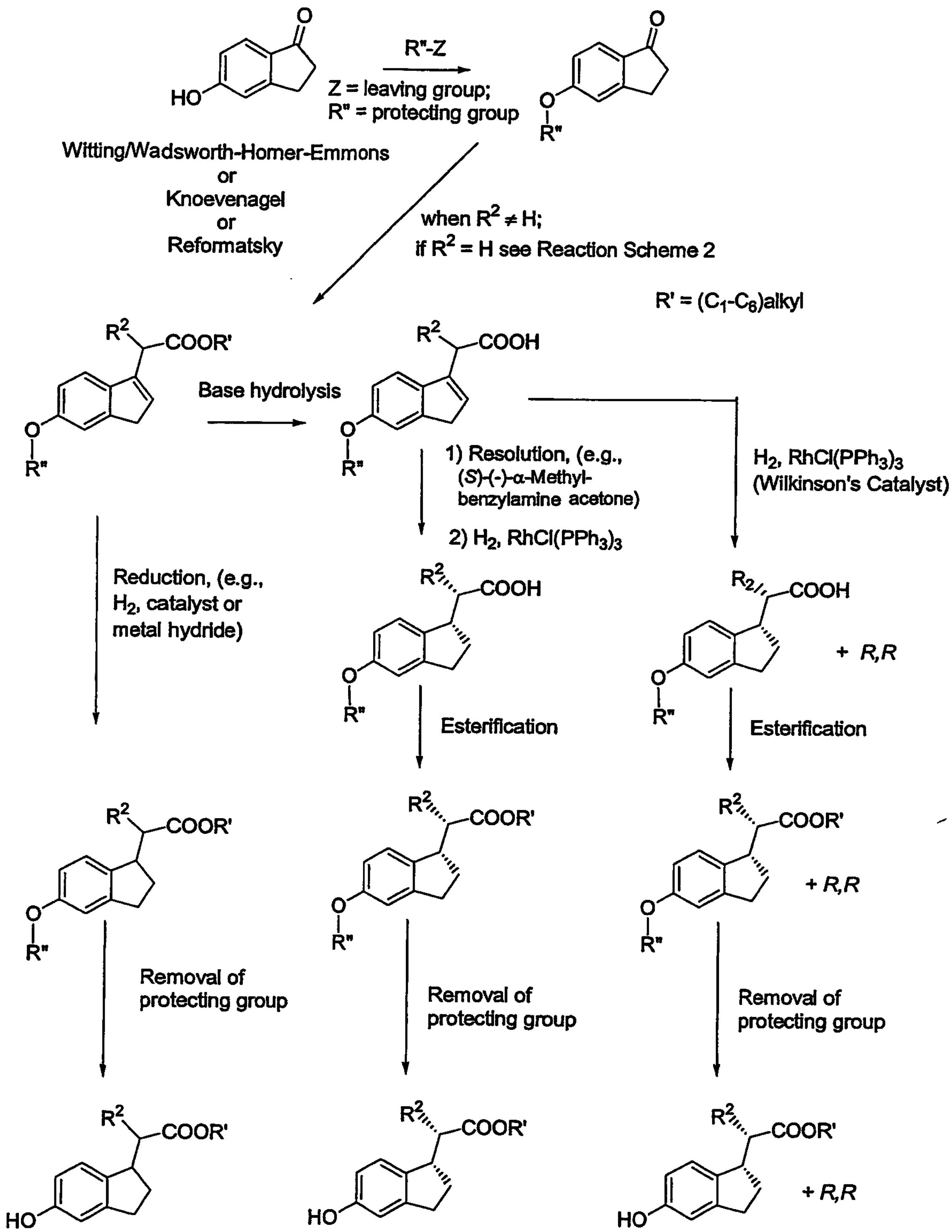
Ac_2O	acetic anhydride
ADDP	1,1'-(azodicarbonyl)dipiperidine
AIBN	2,2'-azobiisobutronitrile
anhy	anhydrous
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binapthyl
BOC	*tert*-butoxycarbonyl
n-BuOH	*n*-butanol
t-BuOH	*tert*-butanol
t-BuOK	potassium *tert*-butoxide
CDI	carbonyl diimidazole
CD_3OD	methanol-d_4
Celite®	diatomaceous earth filter agent, ®Celite Corp.
CH_2Cl_2	methylene chloride
CI-MS	chemical ionization mass spectroscopy
conc	concentrated
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
dec	decomposition
DIA	diisopropyl amine
DMAP	4-(*N,N*-dimethylamino)pyridine
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
ee	enantiomeric excess
EI-MS	electron impact mass spectroscopy
ELSD	evaporative light scattering detector
ES-MS	electrospray mass spectroscopy
EtOAc	ethyl acetate
EtOH	ethanol (100%)
Et_2O	diethyl ether

Et_3N	triethylamine
EtSH	ethane thiol
GC-MS	gas chromatography-mass spectroscopy
h	hour(s)
HPLC	high performance liquid chromatography
LAH	lithium aluminum hydride
LC-MS	liquid chromatography-mass spectroscopy
LDA	lithium diisopropylamide
MeOH	methanol
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMM	4-methylmorpholine
Ph_3P	triphenylphosphine
$Pd(dppf)Cl_2$	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
$Pd(OAc)_2$	palladium acetate
$P(O)Cl_3$	phosphorous oxychloride
Rf	retention factor (TLC)
RT	retention time (HPLC)
rt	room temperature
TEA	triethyl amine
TBDPSCl	*tert*-butyldiphenylsilylchloride
THF	tetrahydrofuran
TFA	trifluoroacetic acid
TLC	thin layer chromatography
TMAD	N^1,N^1,N^2,N^2-tetramethyl-1,2-diazenedicarboxamide

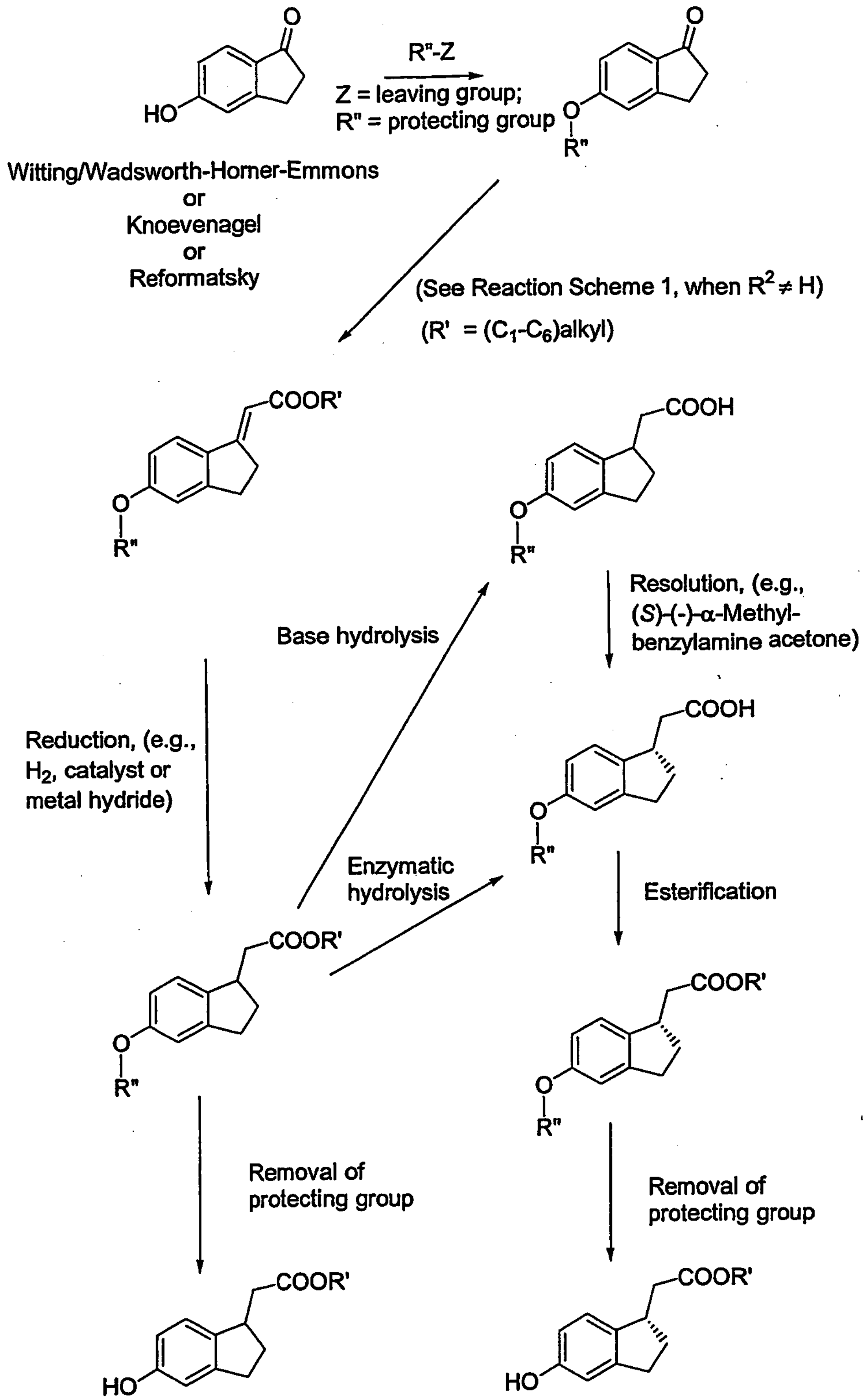
[044] Reaction Schemes 1 and 2 below depict the various synthetic methods used to prepare the starting materials for indane derivatives. Specifically, these methods were used to prepare Intermediates A-E as described below.

Preparation of Indane Starting Materials

[045] **Reaction Scheme 1**

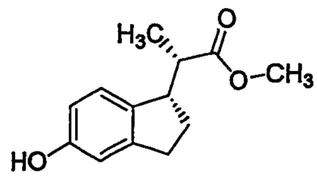


[046] **Reaction Scheme 2**

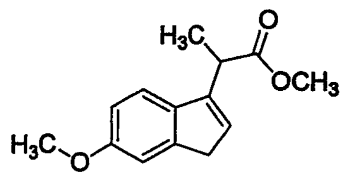


Intermediate A

[047] Preparation of methyl (2*S*)-2-[(1*S*)-5-hydroxy-2,3-dihydro-1*H*-inden-1-yl]propanoate

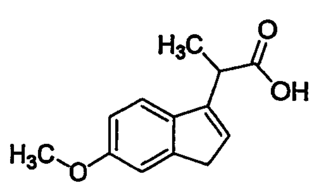


[048] Step 1. Preparation of methyl 2-(6-methoxy-1*H*-inden-3-yl)propanoate



[049] In an oven dried 3-neck 5.0 L flask fitted with a condenser, a thermometer, and an addition funnel was charged under argon, 5-methoxy-1-indanone (86.73 g, 0.52 mol) and THF (2.13 L). The mixture was stirred at rt and became an orange-colored solution. Zinc granules (59.96 g, 0.92 mol, 30 mesh) were added to this solution. The mixture was heated to ~50°C with simultaneous addition of a solution of methyl-2-bromopropionate (88.80 g, 0.79 mol) in THF (393 mL). The reaction mixture was heated for a period of 20 h, after which heating was stopped and the reaction mixture cooled to rt followed by cooling on an ice bath. The mixture was then slowly quenched with HCl (3.3 L, 1N aqueous solution) maintaining the internal temperature at ~18°C. The aqueous layer was extracted with EtOAc (3 x 500 mL). The organic layer was then washed with water (4 x 500 mL, a pH of ~4.5 achieved), brine (500 mL), and dried over Na_2SO_4. The solvent was removed under vacuum to give a dark brown colored oil. The crude product was purified by silica gel chromatography (1-8% EtOAc/ hexane gradient) to give 54.09 g (52%) of the title compound as a dark brown oil. ^{1}H NMR (400 MHz, DMSO-d6): δ 7.25 (1H, d), 7.09 (1H, s), 6.87 (1H, dd), 6.24 (1H, s), 3.82 (1H, q), 3.75 (3H, s), 3.58 (3H, s), 3.30 (2H, s), 1.21 (3H, d); LC-MS: RT = 3.00 min, M+H$^+$: 233.0.

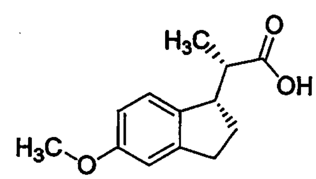
[050] Step 2. Preparation of 2-(6-methoxy-1*H*-inden-3-yl)propanoic acid



[051] In a 1.0 L three-neck flask charged with NaOH (18.57 g, 0.464 mol) and water (216 mL), was slowly added (over 15-20 minutes) a solution of methyl 2-(6-methoxy-1*H*-inden-

3-yl)propanoate (from Step 1, 53.92 g, 0.232 mol) in MeOH (215 mL). During the addition, the reaction temperature increased to 38°C. To this mixture was added THF (108 mL), and then the mixture was heated to 40-45°C for a period of 8 h and subsequently stirred at rt for 17 h. The solvent was removed under vacuum and the resulting aqueous mixture was extracted with CH_2Cl_2 (3 x 100 mL). The aqueous layer was acidified with HCl (38 mL, 37% aqueous solution) to pH ~2.5 and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with water (4 x 150 mL) and brine (50 mL), dried over Na_2SO_4, and filtered. The solvent was evaporated under vacuum and the resulting oil was dried under vacuum at 40-45°C for 16-18 h to give 45.71 g (90%) of the title compound. ^1H NMR (400 MHz, DMSO-d6): δ 7.25 (1H, d), 7.05 (1 H, s), 6.83 (1H, dd), 6.19 (1H, s), 3.73 (3H, s), 3.68 (1H, q), 3.30 (2H, s), 1.39 (3H, d); LC-MS: RT = 2.43 min, $(M+H)^+$: 219.1.

[052] Step 3. Preparation of (2*S*)-2-[(1*S*)-5-methoxy-2,3-dihydro-1*H*-inden-1-yl]propanoic acid

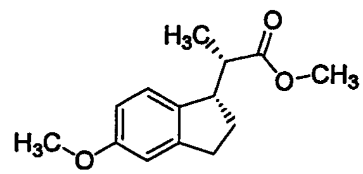


[053] In a 1.0 L single neck flask was charged the racemic 2-(6-methoxy-1*H*-inden-3-yl)propanoic acid (from Step 2, 41.88 g, 0.192 mol) and acetonitrile (629 mL). To this dark orange colored solution was added under stirring (*R*)-(+)-α-methylbenzylamine (25.91 mL, 0.201 mol) slowly over a period of 10 minutes. The dark orange colored solution was then stirred at rt for 16-18 h. The resulting suspension was concentrated to dryness under vacuum to give 61.32 g of the 1:1 diastereomeric salt mixture. Under argon, ethanol (19 mL) was added to chlorotris(triphenylphosphine)rhodium(I) (Wilkinson's Catalyst) (2.0 g, 2.2 mmol). To this suspension was added a solution of the above 1:1 diastereomeric salt mixture (15.0 g, 0.044 mol) in a mixture of EtOH (116 mL) and THF (15 mL). This mixture was hydrogenated in a Parr apparatus under 60 psi at rt over a period of 17 h. The resulting suspension was cooled to 0-5°C over a period of 30 minutes. The precipitate was filtered off and dried under vacuum at 40-45°C for a period of 16-18 h to give the diastereomerically enriched salt (6.79 g, 45%) containing mainly the (*S,S*)-enantiomer of its anionic component [84% *ee*, chiral analytical HPLC, Method B]. The assignment of the absolute configuration is described below. This crude salt was recrystallized by dissolution in MeCN (238 mL) under reflux condition. The resulting solution was cooled over 2 h and the precipitate filtered off, washed with MeCN (13 mL),

and dried under vacuum at 40-45°C to give the desired salt (5.19 g, 76% of mass recovered) having an *ee* of 98.14% [chiral analytical HPLC, Method B] reflecting the identical enantiomeric purity of the (*S,S*)-enantiomer of its anionic component. ^{1}H NMR (of the salt) (400 MHz, DMSO-d6): δ 7.35 (2H, d), 7.30 (2H, t), 7.19 (1H, m), 7.05 (1H, d), 6.73 (1H, s), 6.65 (1H, dd), 4.07 (1H, q), 3.70 (3H, s), 3.40 (1H, q), 2.77 (2H, m), 2.58 (1H, q), 2.05 (1H, m), 1.75 (1H, m), 1.35 (3H, d), 0.87 (3H, d); Quattro Micro (Micromass)(-esi) $(M-H)^-$: 219 (free acid).

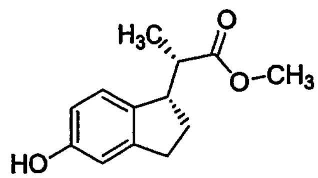
[054] The absolute stereochemistry of the title compound was determined to be (1*S*,2*S*) by single crystal x-ray crystallography of the (*R*)-(+)-α-methyl benzylamine salt. A dichloromethane solution of the diastereomerically pure salt was acidified by washing with 1N HCl followed by washing the organic layer with water. The organic layer was dried with Na_2SO_4 and concentrated to dryness to give the enantiomerically pure free acid, (2*S*)-2-[(1*S*)-5-methoxy-2,3-dihydro-1*H*-inden-1-yl]propanoic acid.

[055] <u>Step 4. Preparation of methyl (2*S*)-2-[(1*S*)-5-methoxy-2,3-dihydro-1*H*-inden-1yl]propanoate</u>



[056] A suspension of (2*S*)-2-[(1*S*)-5-methoxy-2,3-dihydro-1*H*-inden-1-yl]propanoic acid (from Step 3, 6.45 g, 0.029 mol), sodium bicarbonate (7.380 g, 0.088 mol), and iodomethane (5.5 mL, 0.088 mol) in DMF (60 mL) was stirred at rt for a period of 17 h. The completion of the reaction was achieved by addition of an additional amount of iodomethane (0.93 mL, 0.015 mol) and stirring for another 3 h at rt. The reaction mixture was poured into water (200 mL) and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with NaOH (1N aqueous solution), water and brine, dried (Na_2SO_4), filtered, and concentrated to dryness under vacuum to give 5.70 g (84%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d6) δ 6.96 (d, 1H), 6.77 (d, 1 H), 6.67 (dd, 1H), 3.70 (s, 3H), 3.63 (s, 3H), 3.38 (q, 1H), 2.78 (m, 3H), 2.08 (m, 1H), 1.78 (m, 1H); LC-MS RT = 3.10 min; $(M+H)^+$ 234.9.

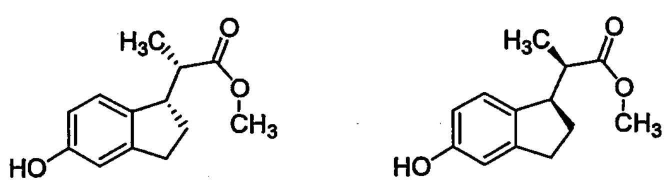
[057] Step 5. Preparation of methyl (2*S*)-2-[(1*S*)-5-hydroxy-2,3-dihydro-1*H*-inden-1-yl]propanoate



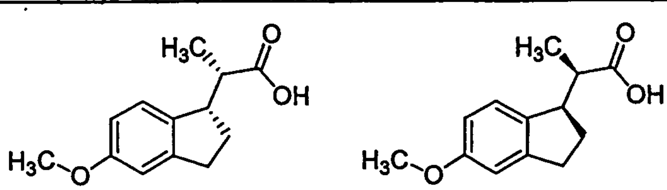
[058] A solution of methyl (2*S*)-2-[(1*S*)-5-methoxy-2,3-dihydro-1*H*-inden-1yl]propanoate (from Step 4, 5.70 g, 0.024 mol) in CH_2Cl_2 (70 mL), under argon, was cooled to 0-5°C and $AlCl_3$ (16.22 g, 0.122 mol) was added portion-wise while maintaining the temperature below 10°C. To this mixture was added EtSH (9.0 mL, 0.122 mol) and the resulting mixture was stirred at 0-5°C for 4 h. The reaction mixture was then slowly poured into vigorously stirred ice-water (200 mL) and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water, brine, dried (Na_2SO_4), filtered, and concentrated to dryness under vacuum. The resulting crude product was purified by silica gel flash chromatography (gradient of 10-40% ethyl acetate/hexanes) to give 4.2 g (80%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.93 (d, 1H), 6.70 (s, 1H), 6.63 (dd, 1H), 3.72 (s, 3H), 3.50 (q, 1H), 2.83 (m, 3H), 2.19 (m, 1H), 1.90 (m, 1H), 1.08 (d, 3H); GC-MS: RT = 8.60 min, $(M+H)^+$ 220.

Intermediate B

[059] Preparation of methyl (2S)-2-[(1S)-5-hydroxy-2,3-dihydro-1*H*-inden-1-yl]propanoate and methyl (2R)-2-[(1R)-5-hydroxy-2,3-dihydro-1*H*-inden-1-yl]propanoate



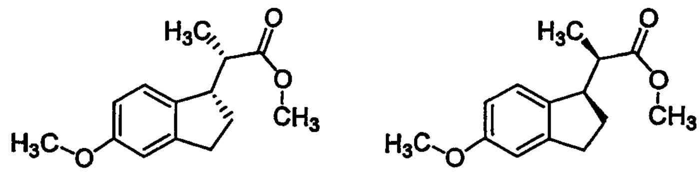
[060] Step 1. Preparation of (2*S*)-2-[(1*S*)-5-methoxy-2,3-dihydro-1*H*-inden-1-yl]propanoic acid and (2*R*)-2-[(1*R*)-5-methoxy-2,3-dihydro-1*H*-inden-1-yl]propanoic acid



[061] The starting acid (Step 2, Intermediate A was reacted under Wilkinson's hydrogenation conditions (60 psi) using 4.5 g starting material, 1.04 g catalyst, and 4.5

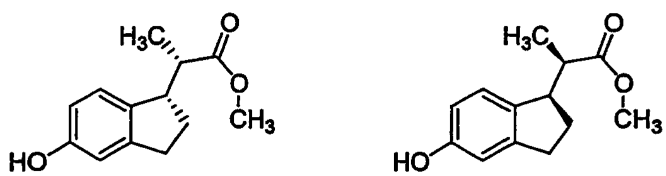
mL triethylamine in 45 mL ethanol and 5 mL THF (analogous procedure to Step 3, Intermediate A, after the salt resolution). The standard extractive workup gave 3.22 g product. ^{1}H NMR (400 MHz, DMSO-d6) 0.87 (d, 3H), 1.75 (m, 1H), 2.04 (m, 1H), 3.66 (s, 3H), 6.65 (m, 1H), 6.76 (s, 1H), 7.04 (d, 1H) 12.18 (bs, 1H); LC-MS RT 2.41 min.

[062] Step 2. Preparation of methyl (2*S*)-2-[(1*S*)-5-methoxy-2,3-dihydro-1*H*-inden-1-yl]propanoate and methyl (2*R*)-2-[(1*R*)-5-methoxy-2,3-dihydro-1*H*-inden-1-yl]propanoate



[063] The compound was prepared by the reaction of 1.5 g starting acid (from Step 1) iodomethane (0.93 mL), and sodium bicarbonate (1.75 g) in 10 mL methanol under the esterification conditions as described in Step 4, Intermediate A. Workup gave 1.53 g, 96%. ^{1}H NMR (400 MHz), (CD_2Cl_2): δ 1.05 (d, 3H), 1.88 (m, 1H), 2.19 (m, 1H), 3.44 (m, 1H), 3.68 (s, 3H), 3.77 (s, 3H).

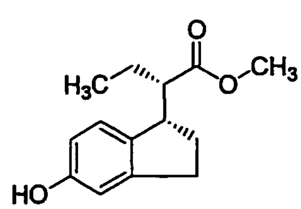
[064] Step 3. Preparation of methyl (2S)-2-[(1*S*)-5-hydroxy-2,3-dihydro-1*H*-inden-1-yl]propanoate and methyl (2R)-2-[(1R)-5-hydroxy-2,3-dihydro-1*H*-inden-1-yl]propanoate



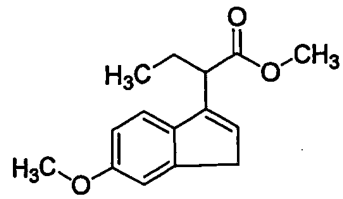
[065] Using the demethylation conditions described in Step 5, Intermediate A and starting with the product of Step 2 (1.53 g), $AlCl_3$ (4.35 g) and EtSH (2.4 mL) in CH_2Cl_2 (20 mL), 1.21 g of product (84%) was obtained. ^{1}H NMR (CD_2Cl_2): δ 1.05 (d, 3H), 1.88 (m, 1H), 2.18 (m, 1H), 3.45 (m, 1H), 3.67 (s, 3H), 6.60 (m, 1H, aryl), 6.69 (s, 1H), 6.93 (d, 1H).

Intermediate C

[066] Preparation of methyl (2*S*)-2-[(1*S*)-5-hydroxy-2,3-dihydro-1*H*-inden-1-yl]butanoate

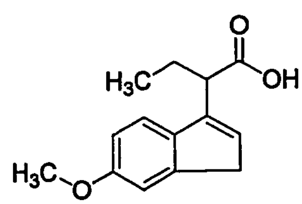


[067] Step 1. Preparation of methyl 2-(6-methoxy-1*H*-inden-3-yl)butanoate



[068] An oven dried 5.0 L four-necked round-bottomed flask was fitted with a thermometer, a condenser, an addition funnel, and a mechanical stirrer. Under an argon atmosphere, a suspension of 5-methoxy-1-indanone (80.0 g, 494 mmol) and Zn powder (Lancaster, 56.2 g, 865 mmol) in THF (2 L, anhydrous) was stirred at 60°C (internal temperature), while a solution of methyl bromobutyrate (134.1 g, 741 mmol) in THF (400 mL, anhydrous) was added slowly using an addition funnel. After completion of the addition, the reaction mixture was stirred at 60°C (internal temperature) for 1 h. The reaction was analyzed by TLC, and once complete, followed by a 1N aqueous HCl workup. After the reaction was completed, it was cooled in an ice-water bath followed by slow addition of HCl (3 L, 1N aqueous solution). The internal temperature was kept below 20°C. The mixture was then extracted with EtOAc (1 L). The organic layer was washed with water until pH 6.0-7.0, then with brine, dried over Na_2SO_4, and filtered. The product (127g, >99%), a yellow oil, was obtained after solvent removal and drying under vacuum. ^1H NMR (300 MHz), (DMSO-d6) δ 7.28 (d, 1H), 7.05 (d, 1H), 6.82 (dd, 1H), 6.22 (s, 1H), 3.72 (s, 3H), 3.60 (m, 1H), 3.58 (s, 3H), 3.28 (s, 2H), 1.95 (m, 1H), 1.80 (m, 1H), 0.88 (t, 3H).

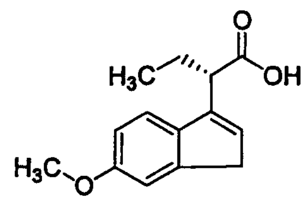
[069] Step 2. Preparation of 2-(6-methoxy-1*H*-inden-3-yl) butanoic acid



[070] To a solution of the ester prepared in Step 1 (200 g, 813 mmol) in MeOH (2 L), was added a solution of KOH (91.0 g, 1.63 mol) in water (200 mL). The reaction mixture was stirred at 60°C (internal temperature) for 2 h. TLC showed 70% conversion. A solution of KOH (45.0 g, 0.81 mol) in water (100 mL) was then slowly added to the reaction mixture. The reaction was complete in 1 h, after which the mixture was cooled to rt, and then the solvents were removed at under reduced pressure. The residue was dissolved in water (3 L), and then washed with EtOAc (2 x 1 L). The aqueous layer was cooled in an ice-water bath, acidified with HCl (37% aqueous solution) to pH < 3.0, and extracted with

CH_2Cl_2 (3 L). The organic phase was washed with water (2 x 1 L), dried over Na_2SO_4, filtered, and then the filtrate was stirred with 30.0 g charcoal for 2 h. The charcoal was removed by filtration through a pad of Celite® to provide the title compound (175 g, 93%) as a light brown solid after solvent removal and drying under reduced pressure. ^1H NMR (300 MHz), (DMSO-d6) δ12.20 (b, 1H), 7.30 (d, 1H), 7.06 (d, 1H), 6.82 (dd, 1H), 6.22 (s, 1H), 3.75 (s, 3H), 3.45 (t, 1H), 3.30 (s, 2H), 1.90 (m, 1H), 1.78 (m, 1H), 0.90 (t, 3H).

[071] Step 3. Preparation of (2*S*)-2-(6-methoxy-1*H*-inden-3-yl)butanoic acid



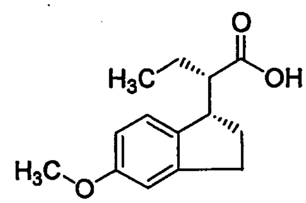
[072] To a solution of the racemic indene acid prepared in Step 2 (300 g, 1.29 mol) in CH_3CN (4.5 L), was added quinine (324 g, 1.0 mol) at rt. The mixture was stirred for 1 h, and became a homogeneous solution. A small amount of the insoluble particles was removed by filtration through a microfiber filter under vacuum. The filtrate was then mechanically stirred under argon for 24 h, a precipitate formed, after which a small sample of the solid was taken and analyzed by chiral analytical HPLC (Method A), showing 76% *ee*. The agitation was continued for two additional days, after which the suspension was filtered. The solid collected was washed with CH_3CN (3 x 200 mL), and then dried under vacuum at 40°C for 3 h. This solid was stirred with CH_3CN (4.5 L) at 70°C until all solids went into solution. Heat was shut off, and the solution was allowed to cool to rt slowly. The resulting suspension was stirred at rt for 24 h and then filtered. The filter cake was washed with CH_3CN (3 x 250 mL) and dried under vacuum at 40°C for 24 h. This quinine salt was collected as a white solid (254.6 g, 35.4% yield, 96.8% *ee* for the acid).

[073] The quinine salt (544.3 g, 0.98 mol) was dissolved in CH_2Cl_2 (4.0 L) to obtain a clear solution. This solution was stirred vigorously with HCl (4.0 L of 2N aqueous solution) in a 22-L round-bottomed flask with a bottom valve. After 30 minutes, the mixture was allowed to settle, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (1 L). The combined organic layers were washed with water (3 x 2.0 L) until pH 5.0-6.0, and then dried over Na_2SO_4. The product (230.8 g, 99%, 96.8% *ee*) was obtained as an off white solid after solvent removal and vacuum drying. The ^1H NMR spectrum was identical to that of the racemic material described Step 2.

[074] Treatment of the mother liquor in similar fashion gave the enriched *R*-isomer. Alternatively, the mother liquor could be subjected to aqueous basic conditions in order to effect racemization and recovery of racemic starting material.

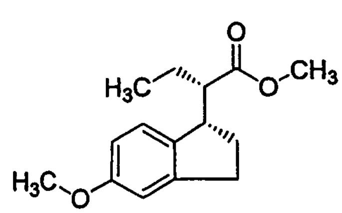
[075] The absolute configuration was determined after Step 4 below.

[076] Step 4. Preparation of (2*S*)-2-[(1*S*)-5-methoxy-2,3-dihydro-1*H*-inden-1-yl]butanoic acid



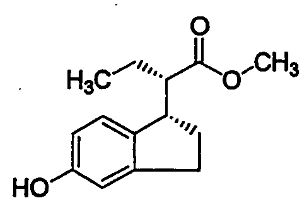
[077] A solution of the product obtained in Step 3 (105 g, 453 mmol), $ClRh(PPh_3)_3$ (21.0 g, 22.7 mmol), and Et_3N (68.8 g, 679.5 mmol) in EtOH (945 mL) and THF (105 mL) was shaken in a 2-L pressure bottle under H_2 (60 psi) for 16 h. The solvents were removed under reduced pressure and the residue was taken up in a mixture of HCl (1.5 L, 1N aqueous solution) and CH_2Cl_2 (1.5 L) and stirred. The aqueous layer was extracted with CH_2Cl_2 (2 x 250 mL). The combined organic layers were washed with HCl (1 L, 1N aqueous solution) and stirred with NaOH (1 L, 1N aqueous solution). The organic layer was extracted with NaOH (2 x 0.5 L, 1N aqueous solution). The combined aqueous layer was washed with CH_2Cl_2 (2 x 250 mL), and acidified (pH 2.0-3.0) by a slow addition of HCl (37% aqueous solution) maintaining the temperature below 15°C. The acidic mixture was extracted with CH_2Cl_2 (2 x 1.5 L). The combined organic phases were washed with water (2 x 0.5 L) until pH 5.0-6.0 and brine, dried over Na_2SO_4, filtered, and then concentrated under reduced pressure. The product (101.0 g, 95% yield, 96.8% *ee*) was obtained as a light yellow oil. The absolute configuration of the title compound was determined by single crystal X-ray crystallography of the corresponding (*R*)-(+)-α-methyl benzylamine salt. ^1H NMR (300 MHz), (DMSO-d6) δ 12.20 (s, 1H), 7.04 (d, 1H), 6.78 (d, 1H), 6.66 (dd, 1H), 3.70 (s, 3H), 3.28 (m, 1H), 2.72 (m, 2H), 2.32 (m, 1H), 2.06 (m, 1H), 1.80 (m, 1H), 1.50 (m, 1H), 1.36 (m, 1H), 0.82 (t, 3H).

[078] Step 5. Preparation of methyl (2*S*)-2-[(1*S*)-5-methoxy-2,3-dihydro-1*H*-inden-1-yl]butanoate



[079] A suspension of the acid prepared in Step 4 (220 g, 0.94 mol), $NaHCO_3$ (237 g, 2.82 mol), CH_3I (200 g, 1.41 mol) in DMF (2.0 L) was stirred under argon at rt for 18 h. Adding additional CH_3I (100 g, 0.71 mol) and stirring for an additional 24 h at rt caused completion of the reaction. The reaction mixture was poured into 4.0 L water, and extracted with EtOAc (2 x 2 L). The combined organic layers were sequentially washed with water (2 x 1 L), NaOH (1 L, 1N aqueous solution), water (2 x 1 L), and brine (0.5 L). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the title compound (233 g, 99%) as a light yellow. ^1H NMR (300 MHz, DMSO-d6) δ 6.90 (d, 1H), 6.78 (d, 1H), 6.66 (dd, 1H), 3.70 (s, 3H), 3.60 (s, 3H), 3.20 (m, 1H), 2.80 (m, 2H), 2.40 (m, 1H), 2.08 (m, 1H), 1.80 (m, 1H), 1.58 (m, 1H), 1.40 (m, 1H), 0.80 (t, 3H).

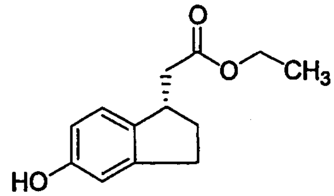
[080] Step 6. Preparation of methyl (2*S*)-2-[(1*S*)-5-hydroxy-2,3-dihydro-1*H*-inden-1-yl]butanoate



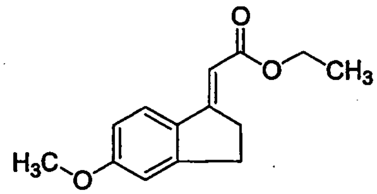
[081] To a cold solution (ice water bath) of the compound prepared in Step 5 (233 g, 0.94 mol) in CH_2Cl_2 (2.5 L), was added $AlCl_3$ (630 g, 4.7 mol) slowly under argon. The internal temperature was kept below 20°C, and the color of the reaction turned purple. EtSH (345 mL, 4.7 mol) was added slowly via an addition funnel maintaining the internal temperature below 15°C. After 2 h of stirring at below 20°C, the reaction was completed and was slowly poured into ice-water (2.5 L) with strong agitation. The organic phase was separated, and the aqueous phases was extracted with CH_2Cl_2 (1 L). The combined organic phases were washed with water (4 x 1 L) until pH 6.0-7.0, and then dried over Na_2SO_4, filtered, concentrated under reduced pressure, and then dried under vacuum to provide the title compound (216 g, 98%) as a white solid. ^1H NMR (300 MHz), (DMSO-d6) δ 9.10 (s, 1H), 6.78 (d, 1H), 6.58 (d, 1H), 6.50 (dd, 1H), 3.60 (s, 3H), 3.20 (q, 1H), 2.70 (m, 2H), 2.40 (m, 1H), 2.08 (m, 1H), 1.80 (m, 1H), 1.50 (m, 2H), 0.80 (t, 3H).

Intermediate D

[082] **Preparation of ethyl [(1*S*)-5-hydroxy-2,3-dihydro-1*H*-inden-1-yl]acetate**

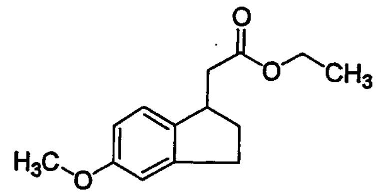


[083] Step1. Preparation of ethyl (5-methoxy-2,3-dihydro-1*H*-inden-1-ylidene)ethanoate



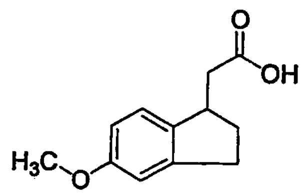
[084] To a solution of 5-methoxyindanone (150 g, 0.91 mol) in anhydrous tetrahydrofuran (4.5 L), was added zinc (30 mesh, 103.64 g, 1.59 mol) and copper(I) chloride (4.53 g, 0.045 mol). The suspension was stirred under argon atmosphere and refluxed for 15 minutes; approximately a 25% portion of ethyl bromoacetate (133 mL, 1.18 mol) was added to the refluxing mixture in a slow dropwise fashion. After allowing to cool and stirring overnight at rt, TLC showed the presence of desired product, indicating the formation of reactive zinc species. The remainder of ethyl bromoacetate was added dropwise; an exotherm was observed (internal temperature increased to 35°C). After 4 h, TLC showed complete reaction. After the solids settled to the bottom of the flask, the liquid was siphoned off leaving a small amount behind to cover the solids. The flask was re-charged with 5-methoxyindanone (157.6 g, 1.86 mol), anhydrous tetrahydrofuran (4.5 L), and zinc (80.92 g, 2.73 mol). Ethyl bromoacetate (140 mL, 2.36 mol) was added dropwise. An exotherm was observed (internal temperature increased to 35°C). When the stirred mixture cooled to rt, TLC showed the reaction to be complete. The solids were allowed to settle and the liquid was siphoned off. The combined reaction solutions were concentrated *in vacuo* to a volume of ~ 2 L. The liquid was then poured into sufficient 1N aqueous hydrochloric acid (cooled in ice water) to bring the pH to 1. The product was extracted with ethyl acetate (2 x 1 L, 1 x 500 mL). The combined extracts were washed with water, brine (1 L each), dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a dark red oil which solidified gradually (438.3 g; theoretical yield = 432 g) ^{1}H NMR ($CDCl_3$): δ 7.5 (d, 1H), 6.8 (m, 2H), 6.2 (t, 1 H), 4.2 (q, 2H), 3.8 (s, 3H), 3.3 (m, 2H), 3.0 (t, 2H), 1.3 (t, 3H). MS (CI) *m/z* 233 $[M+H]^+$.

[085] Step 2. Preparation of ethyl (5-methoxy-2,3-dihydro-1*H*-inden-1-yl)acetate



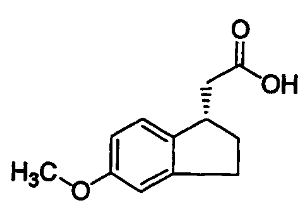
[086] The crude product of Step 1 was dissolved in absolute ethanol (2.6 L) and hydrogenated at 40 psi of hydrogen over 10% palladium on carbon (21.6 g). Filtration through Celite® and concentration of the filtrate afforded 433.3 g of brown oil (99% yield for 2 steps). ^1H NMR ($CDCl_3$): δ 7.1 (dd, 1H), 6.8 (d, 1H), 6.7 (dd, 1H), 4.2 (q, 2H), 3.8 (s, 3H), 3.5 (m, 1H), 2.9 (m, 2H), 2.7 (dd, 1H), 2.4 (m, 2H), 1.7 (m, 1H), 1.3 (t, 3H). MS (CI) *m/z* 235 $[M+H]^+$.

[087] Step 3. Preparation of (5-methoxy-2,3-dihydro-1*H*-inden-1-yl)acetic acid



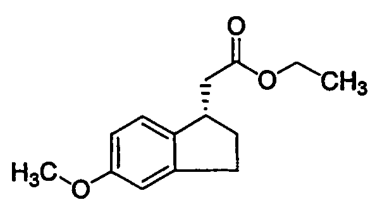
[088] To a solution of the crude ester (416 g, 1.77 mol) prepared in Step 2 in 1 L EtOH, was added a solution of NaOH (142 g, 3.54 mol) in 1.5 L water. The cloudy reaction mixture was heated to reflux, during which time the color changed to dark red, and the reaction became homogeneous.. After 1 h, the reaction was cooled to rt, and the EtOH was removed under reduced pressure. The basic aqueous layer was washed with Et_2O (3 x 500 mL), then acidified with conc. HCl to pH ~4 upon which an oil residue formed. The mixture was extracted with Et_2O (4 x 500 mL). The combined extracts were washed with water (2 x 300 mL), brine, then dried over Na_2SO_4. Filtration and evaporation of solvent under reduced pressure gave the title compound (305 g, 83%) as a yellow solid after overnight drying under vacuum. ^1H NMR ($CDCl_3$): δ 7.34(d, 1H), 6.71(s, 1H), 6.65(dd, 1H), 3.71(s, 3H), 3.47(m, 1H), 2.80(m, 3H), 2.35(m, 2H), 1.71(m, 1H). MS (CI) *m/z* 207 $[M+H]^+$.

[089] Step 4. Preparation of [(1*S*)-5-methoxy-2,3-dihydro-1*H*-inden-1-yl]acetic acid



[090] To a solution of the acid (341.0 g, 1.65 mol) prepared in Step 3 in 8.2 L reagent grade acetone, was added (S)-(-)-α-methylbenzylamine (223.8 mL, 1.74 mol) dropwise at rt with stirring. A thick white precipitate formed during the addition. An additional 500 mL acetone was added and stirring continued for 1 h. The solids were collected by filtration, washed with 300 mL acetone, and dried under suction. The solids were then suspended in acetone (8.2 L) and warmed to reflux until all solids dissolved. The solution was cooled slowly overnight, during which time a white precipitate formed. The suspension was cooled to 0°C, then filtered, and the solids were washed with 500 mL acetone. After drying under suction, a sample analyzed by HPLC showed 95% e.e. The recrystallization process was repeated as above using 6.7 L acetone. HPLC analysis showed 99% e.e. After drying under suction, 192 g salt was obtained. The salt was suspended in 2L EtOAc and 1 L of 1N HCl solution and shaken in a separatory funnel, whereupon the salt dissolved. The organic layer was separated, washed with 1N HCl (500 mL), water (2 x 300 mL), and brine, then dried over Na_2SO_4. The solvent was evaporated under reduced pressure, giving an oil that soon solidified. The title product (120.5 g, 35%) was obtained as an off-white solid after vacuum drying. ^1H NMR ($CDCl_3$): δ 7.10(d, 1H), 6.79(d, 1H), 6.73(dd, 1H), 3.79(s, 3H), 3.55(m, 1H), 2.89(m, 2H), 2.79(dd, 1H), 2.46(dd, 1H), 2.43(m, 1H), 1.80(m, 1H). MS (ESI) *m/z* 207 $[M+H]^+$. The absolute stereochemical assignment was done by single crystal X-ray crystallography on the corresponding Evans oxazolidinone chiral auxiliary.

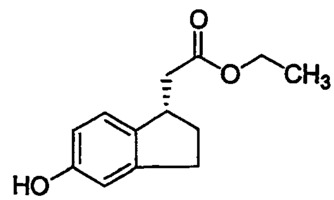
[091] Step 5. Preparation of ethyl [(1*S*)-5-methoxy-2,3-dihydro-1*H*-inden-1-yl]acetate



[092] To a solution of the acid (305 g, 1.48 mol) prepared in Step 4 in 4.8 L absolute EtOH at rt under argon, was added chlorotrimethylsilane (413 mL, 3.25 mol) dropwise. An approximate 5°C rise in temperature was noted during the addition. The reaction was stirred overnight. EtOH was evaporated under reduced pressure, giving a bi-phasic liquid mixture. This was diluted in 500 mL ice-water, then extracted with EtOAc (2 x 750 mL). The combined extracts were washed with water (3 x 300 mL), then with saturated $NaHCO_3$ (200 mL). The organic was washed once more with water (300 mL), then brine, and dried over Na_2SO_4. The title compound (354 g, 102%) was obtained as a light yellow oil after solvent removal and vacuum drying. ^1H NMR ($CDCl_3$): δ 7.07(d, 1H), 6.78(d, 1H),

6.71(dd, 1H), 4.18(q, 2H), 3.78(s, 3H), 3.52(m, 1H), 2.89(m, 2H), 2.72(dd, 1H), 2.37(o, 2H), 1.74(m, 1H), 1.28(t, 3H). MS (CI) *m/z* 235 $[M+H]^+$.

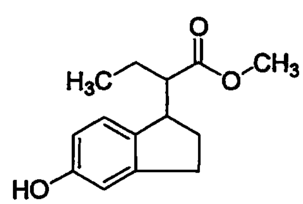
[093] Step 6. Preparation of ethyl [(1*S*)-5-hydroxy-2,3-dihydro-1*H*-inden-1-yl]acetate



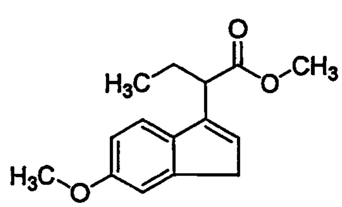
[094] To a cold solution (ice water bath) of the compound prepared in Step 5 (346 g, 1.48 mol) in 4.2 L CH_2Cl_2,was added $AlCl_3$ (984.6 g, 7.38 mol) portionwise under argon such that the reaction temperature was maintained below 10°C. The light brown suspension was stirred 10 minutes, then EtSH (546 mL, 7.38 mol) was added dropwise at such a rate that the reaction temperature was maintained below 5°C. After 2.5 h of stirring below 10°C, the reaction mixture was slowly poured into 6 L ice water with strong agitation. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 1 L). The combined CH_2Cl_2 layers were washed with water (2 x 1 L), then dried over Na_2SO_4. The solvent was removed under reduced pressure, giving a brown oil, which was filtered through a pad of silica gel (eluted with 0-10% EtOAc/Hexanes). Fractions were collected and the title compound (314 g, 96%) was obtained as a thick yellow oil after solvent removal and vacuum drying. ^{1}H NMR ($CDCl_3$): δ 6.92(d, 1H), 6.62(d, 1H), 6.55(dd, 1H), 4.10(q, 2H), 3.43(q, 1H), 2.75(m, 2H), 2.64(dd, 1H), 2.31(dd, 1H), 2.29(m, 1H), 1.67(m, 1H), 1.20 (t, 3H). MS (CI) *m/z* 221 $[M+H]^+$.

Intermediate E

[095] **Preparation of methyl 5-methoxy-2,3-dihydro-1*H*-inden-1-yl butanoate**



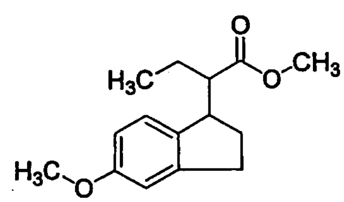
[096] Step 1. Preparation of Methyl 2-(5-methoxy-3*H*-inden-1-yl) butanoate



[097] An oven dried 5.0 L four-necked round-bottomed flask was fitted with a thermometer, a condenser, an addition funnel, and a mechanical stirrer. Under argon

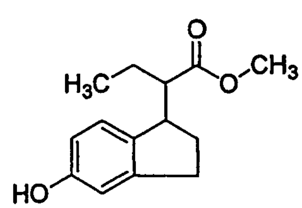
protection, a suspension of 5-methoxy-1-indanone (80.0 g, 494 mmol), zinc powder (Lancaster, 56.2 g, 865 mmol) in 2 L anhydrous tetrahydrofuran was stirred at 60°C (internal temperature), while a solution of methyl bromobutyrate (134.1 g, 741 mmol) in 400 mL anhydrous tetrahydrofuran was added in slowly through an addition funnel. After completion of the addition, the reaction mixture was stirred at 60°C (internal temperature) for 1 h. The reaction was analyzed by TLC after a 1N aqueous hydrochloric acid work-up. After the reaction was completed, it was cooled in an ice-water bath followed by slow addition of 3 L of 1N hydrochloric acid solution. The pot temperature was kept below 20°C. The mixture was then extracted with 1L ethyl acetate. The organic layer was washed with water until pH 6.0-7.0, then saturated sodium chloride solution, and dried over sodium sulfate. Methyl 2-(6-methoxy-1*H*-inden-3-yl) butanoate (127 g, >99%), a yellow oil, was obtained after solvent removal and drying under vacuum. ^{1}H NMR (DMSO-d_6) δ 7.28 (d, 1H), 7.05 (d, 1H), 6.82 (dd, 1H), 6.22 (s, 1H), 3.72 (s, 3H), 3.60 (m, 1H), 3.58 (s, 3H), 3.28 (s, 2H), 1.95 (m, 1H), 1.80 (m, 1H), 0.88 (t, 3H).

[098] Step 2. Preparation of methyl 5-methoxy-2,3-dihydro-1*H*-inden-1-yl butanoate



[099] A solution of methyl 2-(6-methoxy-1*H*-inden-3-yl) butanoate (105 g, 453 mmol), palladium on carbon (10.0 g, 10% eq.) in ethanol (945 mL), and tetrahydrofuran (105 mL) was shaken in a 2-L pressure bottle under 60 psi hydrogen for 16 h. The solvents were removed under reduced pressure. Methyl 5-methoxy-2,3-dihydro-1*H*-inden-1-yl butanoate (101.0 g, 95% yield) was obtained as a light yellow oil. ^{1}H NMR (DMSO-d_6) δ 12.20 (s, 1H), 7.04 (d, 1H), 6.78 (d, 1H), 6.66 (dd, 1H), 3.70 (s, 3H), 3.28 (m, 1H), 2.72 (m, 2H), 2.32 (m, 1H), 2.06 (m, 1H), 1.80 (m, 1H), 1.50 (m, 1H), 1.36 (m, 1H), 0.82 (t, 3H).

[100] Step 3. Preparation of methyl 5-methoxy-2,3-dihydro-1*H*-inden-1-yl butanoate



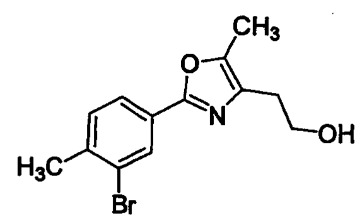
[101] To a cold solution (ice water bath) of methyl 5-methoxy-2,3-dihydro-1*H*-inden-1-yl butanoate (233 g, 0.94 mol) in 2.5 L CH_2Cl_2, was added aluminum trichloride (630 g, 4.7

mol) slowly under argon. The pot temperature was kept below 20°C, and the color of the reaction turned purple. Ethyl thiol (345 mL, 4.7 mol) was added slowly via an addition funnel to the reaction mixture, and the internal temperature was kept below 15°C. After 2 h of stirring at below 20°C, the reaction went to completion by NMR analysis. The pot mixture was slowly poured into 2.5 L ice water with a strong agitation. The organic layer was separated, and the aqueous layer was extracted with 1 L dichloromethane. The combined dichloromethane layers were washed with water (4 x 1 L) until the pH was 6.0-7.0, and then dried over sodium sulfate. Methyl 5-hydroxy-2,3-dihydro-1*H*-inden-1-yl butanoate (216 g, 98%) was obtained as a white solid after solvent removal and vacuum drying. ^{1}H NMR (DMSO-d_6) δ 9.10 (s, 1H), 6.78 (d, 1H), 6.58 (d, 1H), 6.50 (dd, 1H), 3.60 (s, 3H), 3.20 (q, 1H), 2.70 (m, 2H), 2.40 (m, 1H), 2.08 (m, 1H), 1.80 (m, 1H), 1.50 (m, 2H), 0.80 (t, 3H).

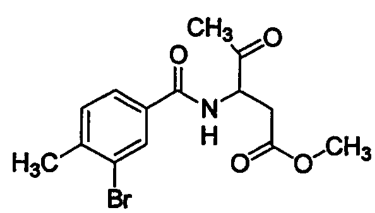
[102] Intermediate F, as described below, was used for the preparation of the oxazole ethanol sub unit.

Intermediate F

[103] **Preparation of 2-[2-(3-bromo-4-methylphenyl)-5-methyl-1,3-oxazol-4-yl]ethanol**



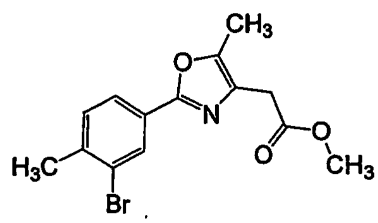
[104] Step 1. Preparation of methyl 3-[(3-bromo-4-methylbenzoyl)amino]-4-oxopentanoate



[105] To a suspension of L-aspartic acid β-methyl ester hydrochloride (Sigma, 5.0 g, 27.23 mmol) in chilled (< 5°C) CH_2Cl_2 (150 mL) was added Et_3N (8.33 g, 81.70 mmol) in a steady flow followed by a slow addition of Me_3SiCl (6.51 g, 59.92 mmol). The mixture was warmed to 25°C and stirred for 1 h, cooled again (< 10°C), and 3-bromo-4-methylbenzoyl chloride (6.36 g, 27.23 mmol) was added dropwise. The mixture was allowed to warm to ambient temperature slowly with stirring for 16 h. The reaction

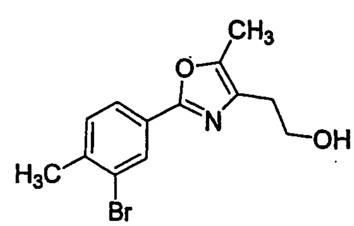
mixture was then diluted with CH_2Cl_2 (150 mL) and washed with 1N HCl (50 mL), brine (50 mL), and dried over Na_2SO_4. The resultant amide product (8.9 g g, 95%), a white solid, was obtained after solvent removal and drying under vacuum. It was then dissolved in pyridine (50 mL), and DMAP (0.17 g, 1.38 mmol) was added. Acetic anhydride (26 mL) was added slowly and then the reaction was heated at 90°C for 2 h. The cooled solution was poured into 200 mL ice water and extracted with EtOAc. The organic layer was washed with 2N HCl (3 x 100 mL) and 1N NaOH (100 mL), dried over $MgSO_4$ and concentrated to afford the title compound as a off white solid which was taken to the next step.

[106] Step 2. Preparation of methyl [2-(3-bromo-4-methylphenyl)-5-methyl-1,3-oxazol-4-yl]acetate



[107] The total crude material prepared in Step 1 was dissolved in acetic anhydride (25 mL) followed by slow addition of conc. H_2SO_4 (1 mL). The pot temperature reached 90°C. The reaction was then held at 90°C for 1 h, cooled, and the acetic anhydride removed *in vacuo*. The residue was poured into ice water (250 mL) and extracted with EtOAc (300 mL total). The organic layer was then extracted with 1N HCl (100 mL), saturated $NaHCO_3$ (100 mL) and brine, separated, then dried with $NaSO_4$ and concentrated to afford the title ester (4.6 g). The crude product was used in the next step.

[108] Step 3. Preparation of 2-[2-(3-bromo-4-methylphenyl)-5-methyl-1,3-oxazol-4-yl]ethanol



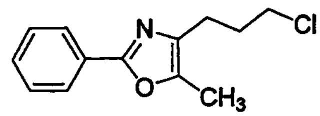
[109] The oxazole ester prepared in Step 2 (4.7 g, 14.5 mmol) was dissolved in THF (20 mL), and $LiBH_4$ (10.15 mL, 20.3 mmol, 2 M solution in THF) was added slowly while maintaining the temperature below 45°C. Upon completion the solvent was reduced to half the volume, and then the reaction mixture was poured into ice water (200 mL). The

mixture was then acidified by slowly adding 1N HCl and the aqueous phase was extracted with ethyl acetate. The organic phase was dried (Na_2SO_4) and filtered, and the solvents were evaporated under vacuum and the residue was purified by Biotage to obtain the desired oxazole alcohol (3.8 g, 87%).

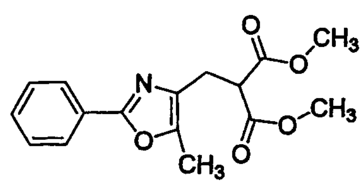
[110] Intermediate G, as described below, was used for the preparation of the oxazole propanol sub unit as exemplified in Reaction Scheme 4.

Intermediate G

[111] **Preparation of 4-(3-chloropropyl)-5-methyl-2-phenyl-1,3-oxazole**

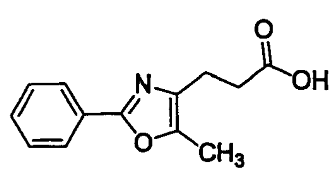


[112] Step1. Preparation of dimethyl 2-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]malonate



[113] To a solution of dimethyl malonate (0.41 mL, 3.61 mmol) in tetrahydrofuran (10 mL) was added sodium hydride (87 mg, 2.41 mmol) followed by addition of 4-(chloromethyl)-5-methyl-2-phenyl-1,3-oxazole (500 mg, 2.41 mmol, commercially available) and heated up to 70°C for 16 h. The reaction mixture was then diluted with 20 mL ice-cold water and extracted with ethyl acetate (30 mL x 3). The combined organic layer was then washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford an oil, which was subjected to the next step without purification.

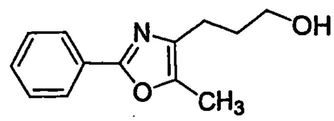
[114] Step 2. Preparation of 3-(5-methyl-2-phenyl-1,3-oxazol-4-yl)propanoic acid



[115] The crude dimethyl 2-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]malonate from the previous step was dissolved in a mixture of concentrated acetic acid (15 mL) and 6 N hydrochloric acid (5 mL). The mixture was then refluxed for 24 h. The mixture was then cooled to rt, concentrated, and made alkaline with aqueous sodium hydroxide. After

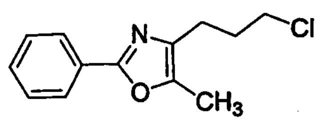
washing with diethyl ether (2 x 20 mL), the aqueous layer was then acidified with acetic acid and extracted with dichloromethane. The combined organic layer was then washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford 369 mg of desired product. ^{1}H NMR (CDCl$_3$-d_1): δ 7.92 (d, 2 H), 7.40-7.53 (m, 3 H), 2.71-2.89 (m, 4 H), 2.38 (s, 3 H).

[116] Step 3. Preparation of 3-(5-methyl-2-phenyl-1,3-oxazol-4-yl)-1-propanol



[117] To a solution of 3-(5-methyl-2-phenyl-1,3-oxazol-4-yl)propanoic acid (369 mg, 1.6 mmol) in tetrahydrofuran (5 mL) was added 1.0 M borane-tetrahydrofuran complex at 0°C under argon. After the addition was complete, the mixture was refluxed with stirring for 16 h. After the mixture was concentrated under reduced pressure, methanol was added dropwise, and the solvent was removed under reduced pressure. The process was repeated three times to ensure the methanolysis of the intermediate borane complex. The residue was then purified by flash chromatography with 10% to 20% ethyl acetate in hexanes to afford 0.34 g (98%) of 3-(5-methyl-2-phenyl-1,3-oxazol-4-yl)-1-propanol. ^{1}H NMR (CDCl$_3$-d_1): δ 7.98 (d, 2 H), 7.32-7.44 (m, 3 H), 3.78 (q, 2 H), 3.38 (t, 1 H), 2.63 (t, 2 H), 2.37 (s, 3 H), 1.91 (q, 2 H).

[118] Step 4. Preparation of 4-(3-chloropropyl)-5-methyl-2-phenyl-1,3-oxazole

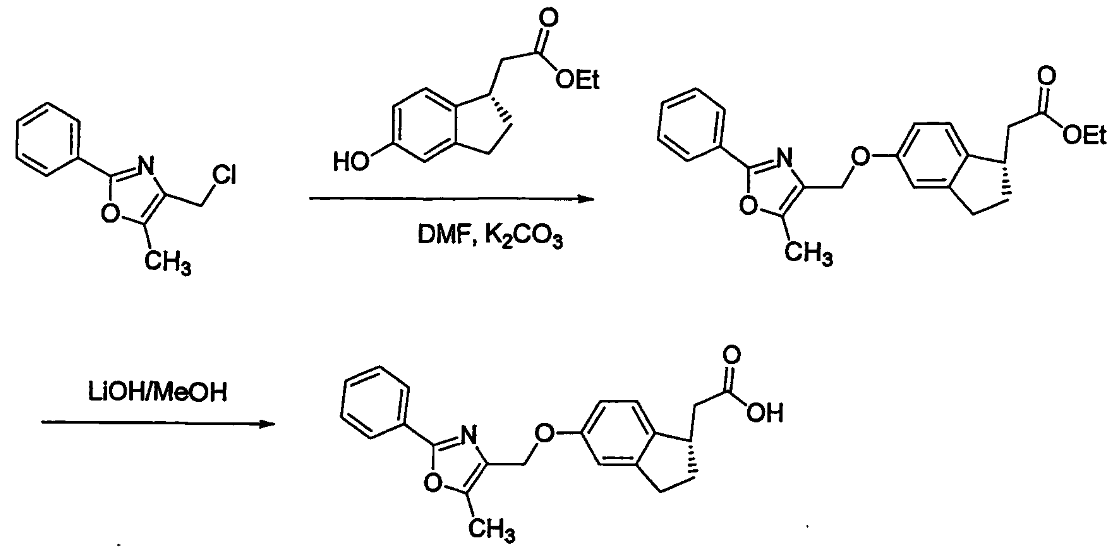


[119] To 3-(5-methyl-2-phenyl-1,3-oxazol-4-yl)-1-propanol (98 mg, 0.45 mmol) in a dried round bottom flask was added thionyl chloride (1 mL) and the mixture was stirred at rt for 30 minutes. The mixture was concentrated under reduced pressure, dichloromethane was carefully added dropwise and the solvent was removed under reduced pressure. Methylene chloride (10 mL) was added and re-evaporated (3x) until a semi-solid crude product was obtained. The solid was used without purification.

[120] **Preparation of Oxazoles**

Reaction Schemes 3-13 below depict the various synthetic methods used to make compounds of Formula (Ia) where X = O. These methods were used to prepare Examples 1-77, as specifically described below.

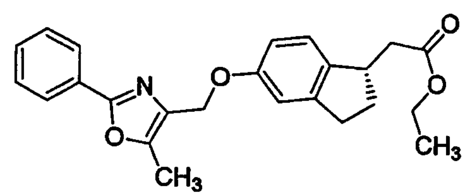
[121] **Reaction Scheme 3**



[122] Using the appropriate starting materials, Examples 1 and 2 were prepared by the method exemplified in Reaction Scheme 3.

[123] **Example 1**

Preparation of ethyl {(1*S*)-5-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate

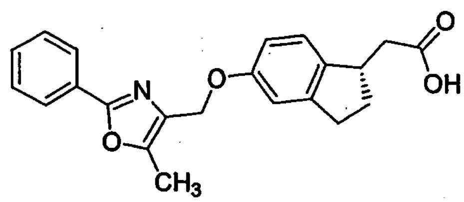


[124] Ethyl [(1S)-5-hydroxy-2,3-dihydro-1*H*-inden-1-yl]acetate (Intermediate D, 210 mg, 0.95 mmol), 4-(chloromethyl)-5-methyl-2-phenyl-1,3-oxazole (198 mg, 0.95 mmol, commercially available), and potassium carbonate (180 mg, 1.33 mmol) was added to 10 mL anhydrous *N,N*-dimethyl formamide and was stirred for 3 h at 80°C under argon. The mixture was poured into 10 mL water, acidified with 1N hydrochloric acid to pH 5, and extracted with 20 mL ethyl acetate (3x). The combined organic layer was washed with water, brine, dried over sodium sulfate, and concentrated under reduced pressure, leaving an oil. The crude product was purified by flash chromatography using 5% to 10% ethyl acetate in hexanes to afford 250 mg (67%) of ethyl {(1S)-5-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate. ^{1}H NMR ($CDCl_3$-d_1): δ 7.59-8.15 (m, 2 H) 7.41-7.51 (m, 3 H), 7.08 (d, 1 H), 6.90 (s, 1 H), 6.81 (d, 1 H), 5.06 (s, 2 H), 4.18

(q, 2 H), 3.42-3.58 (m, 1 H), 2.62-3.98 (m, 3 H), 2.47 (s, 3 H), 2.30-2.45(m, 2 H), 1.60-1.81 (m, 1 H), 1.15 (t, 3 H).

[125] Example 2

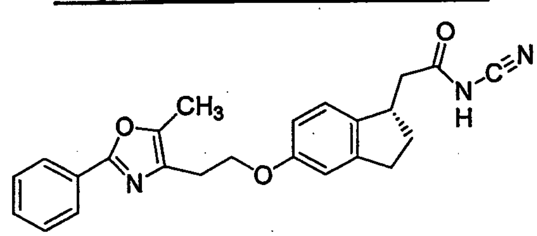
Preparation of {(1S)-5-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic acid



[126] To a solution of ethyl {(1S)-5-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate (50 mg, 0.13 mmol) in 5 mL ethanol was added lithium hydroxide (42 mg, 1 mmol), and the mixture was heated to 40°C for 1 h. The reaction mixture was then allowed to cool to rt and the pH of the solution was adjusted to 5 using 0.5 N hydrochloric acid and the solution was evaporated under reduced pressure to afford 48 mg of the title compound. ^{1}H NMR ($CDCl_3$): δ 7.98 (dd, 2 H), 7.81 (t, 1 H), 7.12-7.25 (m, 2 H), 7.11 (d, 1 H), 6.85 (s, 1 H), 6.78 (d, 1 H), 4.98 (s, 2 H), 3.42-3.60 (m, 1 H), 2.71-2.92 (m, 3 H), 2.28-2.45 (m, 5 H), 1.68-1.83 (m, 1 H); MS (ES) 364 $(M+H)^+$; HPLC RT 3.06 min.

[127] Example 3

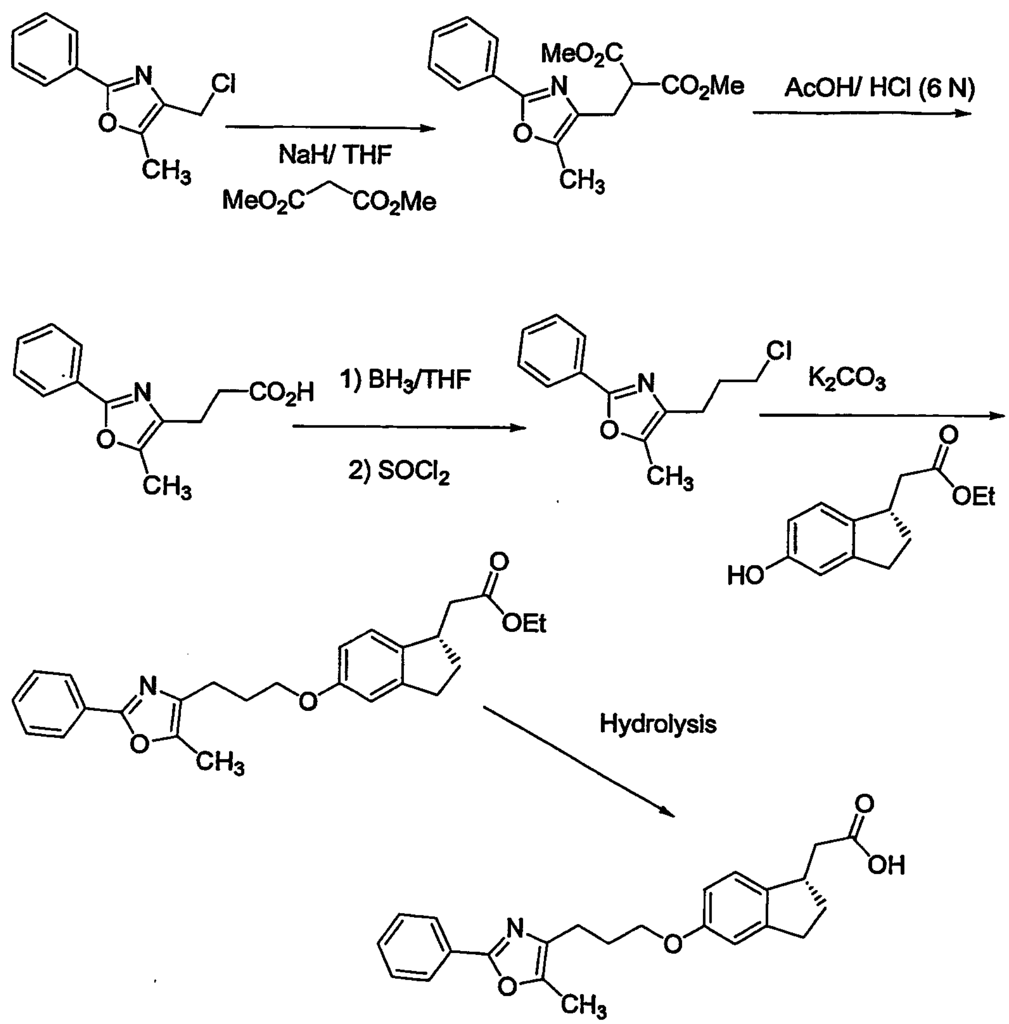
Preparation of *N*-cyano-2-{(1*S*)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetamide



[128] Coupling of Intermediate D with 2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)-1-ethanol (Lancaster) using the method described for Example 12, Step 5 was followed by hydrolysis using the method described in Example 2 to produce {(1*S*)-5-[2-(5-ethyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic acid. This carboxylic acid (60 mg, 0.148 mmol) was dissolved in dichloromethane and to this was added EDCI (43 mg, 0.222 mmol) followed by cyanamide (7 mg, 0.177 mmol). A catalytic amount of DMAP was added, and the resulting solution was stirred at rt for 3 h. The reaction mixture was diluted with 30 mL ethyl acetate and then washed with water, 1N HCl and then with a saturated sodium bicarbonate solution. The organic layer was dried with

magnesium sulfate, filtered and then concentrated via rotary evaporation to yield the title compound as an oil which was purified by column chromatography (dichloromethane/methanol 95/5). ES-MS *m/z* 402.2 $(M+H)^+$); HPLC RT 3.45; ^1H NMR ($CDCl_3$): δ 7.78 (m, 2H), 7.20 (m, 3H), 6.81 (d, 1H), 6.59 (s, 1H), 6.46 (dd, 1H), 3.98 (t, 2H), 3.24 (m, 1H), 3.11 (m, 1H), 2.77 (t, 2H), 2.46-2.63 (m, 2H), 2.20 (m, 5H), 1.51, (m, 1H).

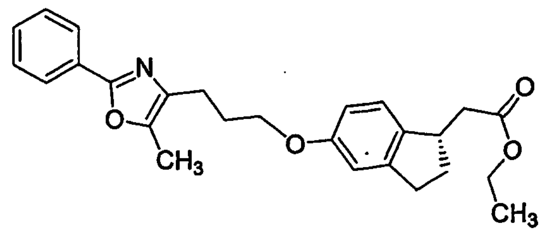
[129] **Reaction Scheme 4**



[130] Using the appropriate starting materials, Examples 4 and 5 were prepared by the method exemplified in Reaction Scheme 4.

[131] **Example 4**

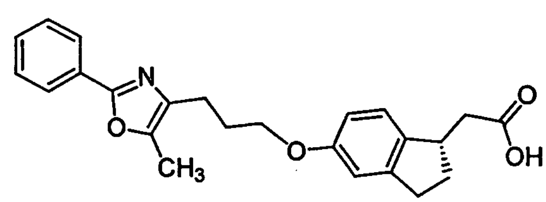
Preparation of ethyl {(1*S*)-6-[3-(5-methyl-2-phenyl-1,3-oxazol-4-yl)propoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate



[132] Ethyl [(1*S*)-5-hydroxy-2,3-dihydro-1*H*-inden-1-yl]acetate (Intermediate D, 80 mg, 0.36 mmol), 4-(3-chloropropyl)-5-methyl-2-phenyl-1,3-oxazole (Intermediate G, 106 mg, 0.45 mmol), and potassium carbonate (310 mg, 2.25 mmol) were added to 5 mL anhydrous *N,N*-dimethyl formamide and the solution was stirred for 16 h at 80°C under argon. The mixture was poured into 10 mL water, acidified with 1N hydrochloric acid to pH 5, and extracted with (20 mL x 3) ethyl acetate. The combined organic layer was washed with water, brine, dried over sodium sulfate, and concentrated under reduced pressure, leaving an oil. The crude material was purified by flash chromatography with 10% to 20% ethyl acetate in hexanes to afford 100 mg (53%) of the title compound. ^{1}H NMR (CDCl$_3$-d_1): δ 7.99 (d, 2H), 7.36-7.39 (m, 3H), 7.06 (d, 1H), 6.79 (s, 1H), 6.72 (d, 1H), 4.18 (q, 2H), 3.95 (t, 2H), 3.51 (q, 1H), 2.68-2.92 (m, 5H), 2.30-2.43 (m, 2H), 2.28 (s, 3H), 2.08-2.21 (m, 2H), 1.69-1.81 (m, 1H), 1.16 (t, 3H); MS (ES) 420 (M+H)$^+$; HPLC RT 4.02.

[133] **Example 5**

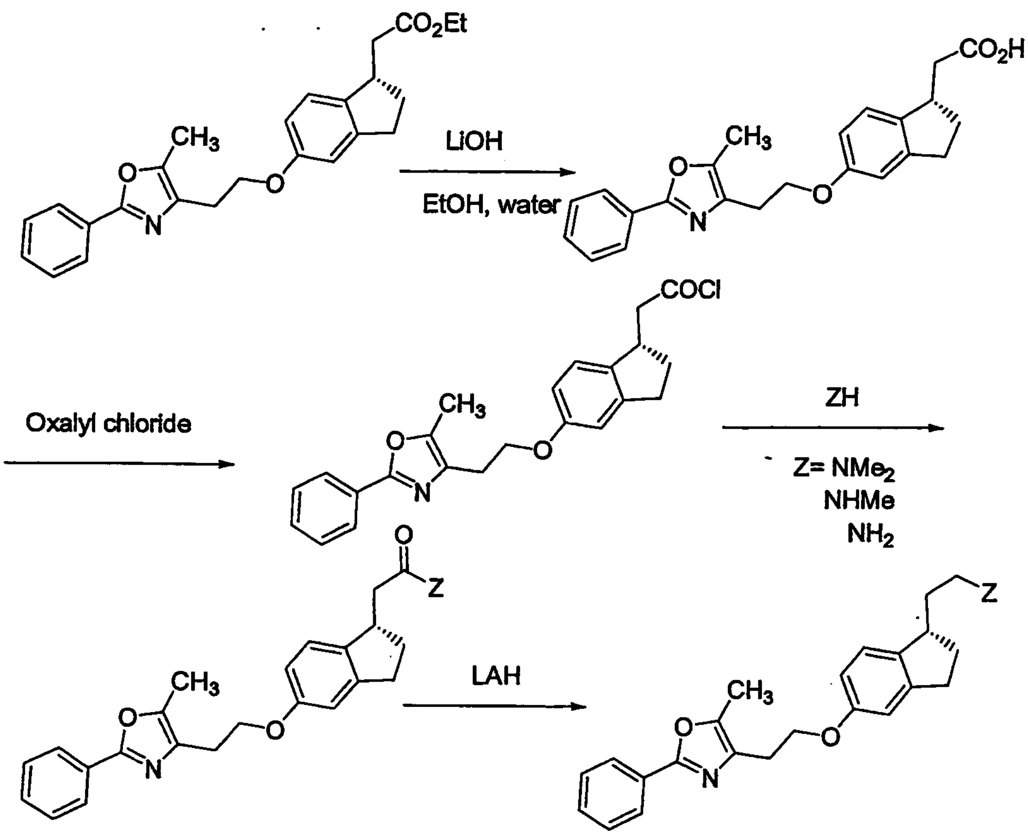
Preparation of {(1*S*)-6-[3-(5-methyl-2-phenyl-1,3-oxazol-4-yl)propoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic acid



[134] To a solution of ethyl {(1*S*)-6-[3-(5-methyl-2-phenyl-1,3-oxazol-4-yl)propoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate (60 mg, 0.14 mmol) in 1 mL ethanol was added lithium hydroxide (20 mg, 1 mmol), and the mixture was heated to 40°C for 1 h. The reaction mixture was then allowed to cool to rt and the pH of the solution was adjusted to 5 using 0.5 N HCl. The solution was removed under reduced pressure to give an oil, which was subjected to HPLC purification (0% to 70% acetonitrile in water) (0.1% TFA) to afford 56.4 mg of desired product. ^{1}H NMR (CDCl$_3$): δ 7.88 (d, 2 H), 7.28-7.40 (m, 3 H), 6.99 (d, 1

H), 6.68 (s, 1 H), 6.62 (d, 1 H), 3.83 (t, 2 H),3.40-3.51 (m, 1 H), 2.52-2.91 (m, 5 H), 2.24-2.42 (m, 2 H), 2.21 (s, 3 H), 1.98-2.16 (m, 2 H), 1.62-1.78 (m, 1 H); MS (ES) 392.6 $(M+H)^+$; HPLC RT 3.41.

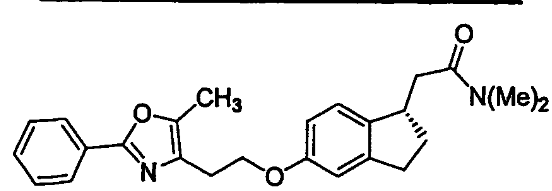
[135] **Reaction Scheme 5**



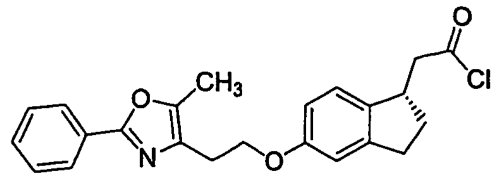
[136] Using the appropriate starting materials, Examples 6-11 were prepared by the method exemplified in Reaction Scheme 5.

[137] **Example 6**

Preparation of *N,N*-dimethyl-2-{(1*S*)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetamide

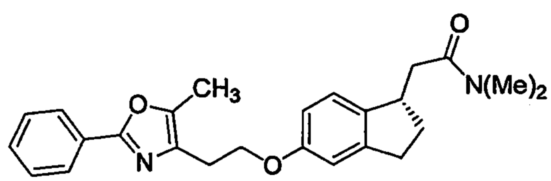


[138] Step 1. Preparation {(1*S*)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetyl chloride



[139] To a solution of (1*S*)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic acid (see material from Example 3 after hydrolysis, 82 mg, 0.48 mmol) in 1 mL CH_2Cl_2 was added thionyl chloride (1 mL), and the mixture was stirred at rt for 30 minutes. After the mixture was concentrated under reduced pressure, dichloromethane was carefully added dropwise and the solvent was removed under reduced pressure. The process was repeated three times until the semi-solid crude product was obtained. The solid was used for the next step without purification.

[140] Step 2. Preparation of *N,N*-dimethyl-2-{(1*S*)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetamide

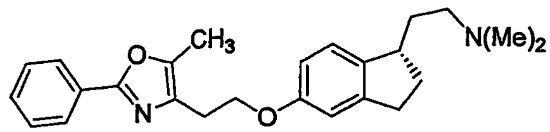


[141] To a 2 M solution of dimethyl amine in THF (10 mL) in a round bottom flask, {(1*S*)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetyl chloride (Step 1, 63 mg, 0.16 mmol) in dichlormethane (20 mL) was added dropwise. The reaction mixture was stirred at rt for 16 h. Solvent was then removed under reduced pressure and the crude product was purified using Gilson-HPLC to afford the titled compound (58 mg, 90%). MS (electrospray) 405.2 $(M+H)^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 7.92-8.00 (m, 2 H), 7.40-7.52 (m, 3 H), 7.04 (d, 1 H), 6.72 (s, 1 H), 6.06 (d, 1 H), 4.19 (t, 2 H), 3.48-3.64 (m, 1 H), 2.62-3.05 (m, 11 H), 2.28-2.46 (m, 5 H), 1.60-1.78 (m, 1 H); MS (ES) 405.2 $(M+H)^+$; HPLC RT 3.26.

[142] **Example 7**

General method for the formation of amides

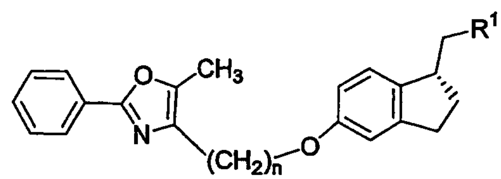
Synthesis *N,N*-dimethyl-2-{(1*S*)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}ethanamine



[143] To a solution of *N,N*-dimethyl-2-{(1*S*)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetamide (40 mg, 0.1 mmol) in tetrahydrofuran (3 mL) was added lithium aluminum hydride (10 mg) at rt. The reaction mixture was then stirred for 12 h. Purification using an HPLC system (0% to 70% of acetonitrile in water) afforded 38 mg of desired product. MS (electrospray) 391.3 $(M+H)^+$; ^1H NMR (300 MHz, $CDCl_3$): δ 7.92-8.00 (m, 2 H), 7.42-7.54 (m, 3 H), 7.09 (d, 1 H), 6.79 (s, 1 H), 6.70 (d, 1 H), 4.21 (t, 2 H), 3.55-3.60 (m, 1 H), 2.69-3.08 (m, 4 H), 2.51-2.64 (m, 2 H), 2.21-2.42 (m, 10 H), 1.95-2.12 (m, 1 H), 1.50-1.72 (m, 2 H); MS (ES) 391.3 $(M+H)^+$; HPLC RT 2.48.

[144] Additional compounds prepared by similar methods are summarized in Table 1 below:

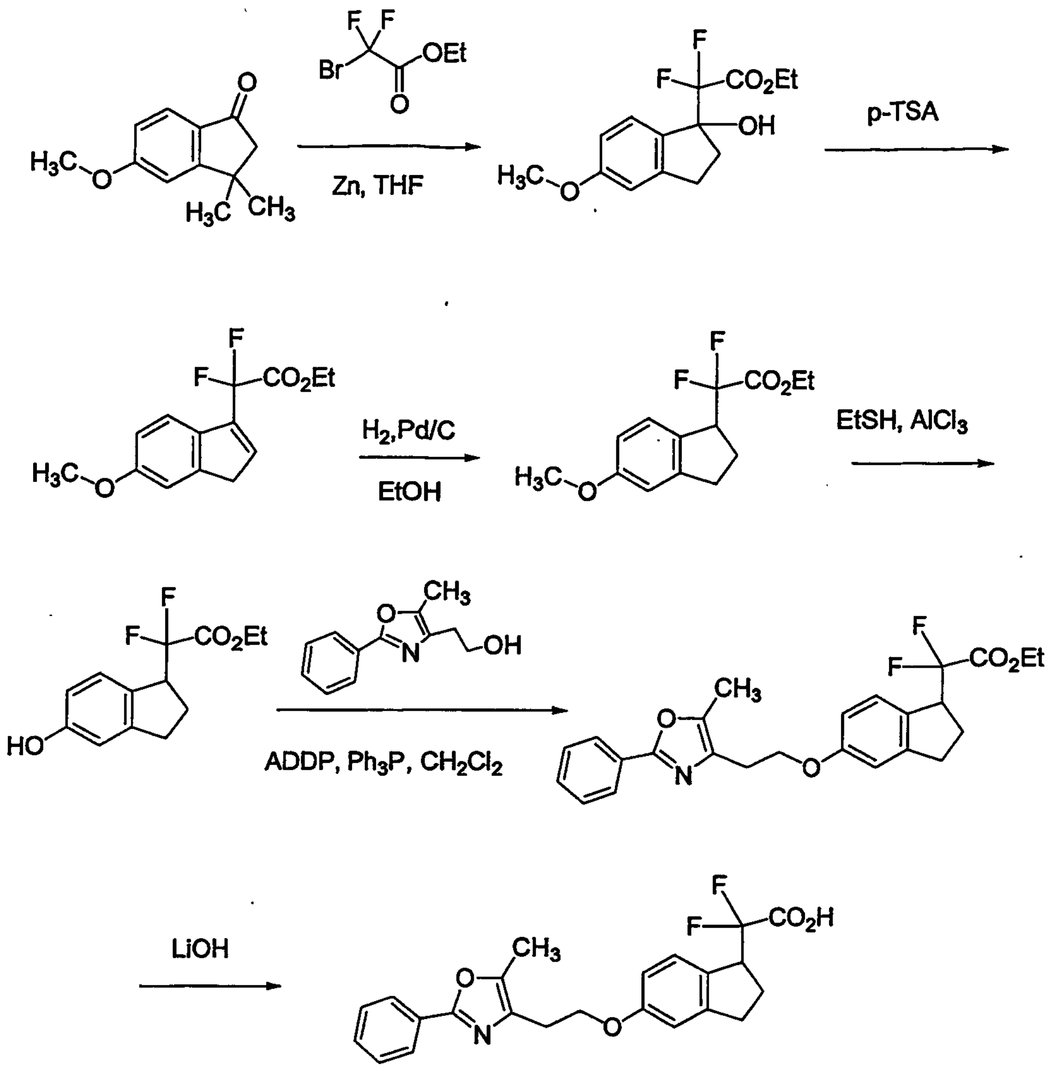
[145] **Table 1**



Example No.	R^1	n	HPLC RT (min)	EI-MS $(M+H)^+$	Name
8	CH_2NH_2	2	2.45	363.2	2-{(1*S*)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}ethanamine
9	$CONH_2$	2	2.91	377.1	2-{(1*S*)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetamide
10	CONHMe	2	3.03	391.1	*N*-methyl-2-{(1*S*)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetamide

Example No.	R^1	n	HPLC RT (min)	EI-MS $(M+H)^+$	Name
11	CH_2NHMe	2	2.49	377.2	*N*-methyl-2-{(1*S*)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}ethanamine

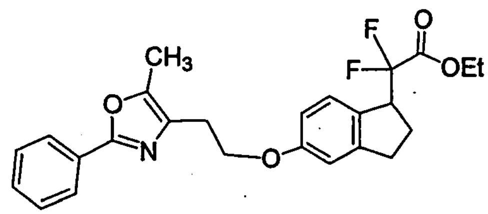
[146] **Reaction Scheme 6**



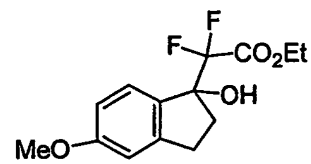
[147] Using the appropriate starting materials, Examples 12 and 13 were prepared by the method exemplified in Reaction Scheme 6.

[148] **Example 12**

Preparation of ethyl difluoro{5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate

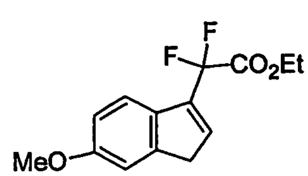


[149] Step 1. Preparation of ethyl difluoro(1-hydroxy-5-methoxy-2,3-dihydro-1*H*-inden-1-yl)acetate



[150] An oven dried 3-necked round-bottomed flask was fitted with a thermometer, a condenser and an addition funnel. Under argon protection, a suspension of 5-methoxy-1-indanone (2.66 g, 16.4 mmol) and Zn powder (Lancaster, 1.87 g, 28.7 mmol) in 100 mL anhydrous THF was stirred at 60°C (internal temperature), while a solution of ethyl bromodifluoroacetate (5.00 g, 24.6 mmol) in 30 mL anhydrous THF was added slowly through an addition funnel. After completion of the addition, the reaction mixture was stirred at 60°C (internal temperature) for 3 h. The reaction mixture was cooled in an ice-water bath followed by slow addition of 125 mL of 1N HCl solution. The pot temperature was maintained below 20°C. The mixture was then extracted with EtOAc. The organic layer was washed with water until pH 6.0-7.0, then saturated NaCl solution, and dried over Na_2SO_4. The product (4.6 g, >99%), a yellow oil, was obtained after solvent removal and drying under vacuum. ^1H NMR ($CDCl_3$): δ 7.38 (d, 1 H), 6.79 (m, 2 H), 4.34 (q, 2 H), 3.81 (s, 3 H), 2.93 (m, 4 H), 2.16 (m, 1H), 1.31 (t, 3 H).

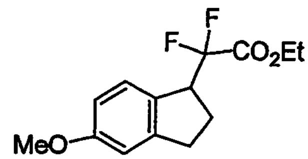
[151] Step 2. Preparation of ethyl difluoro(6-methoxy-1*H*-inden-3-yl)acetate



[152] The product from Step 1 (4.6 g, 17.1 mmol) was placed in a round-bottom flask equipped with a Dean-Stark trap and dry toluene was added, followed by p-toluenesulfonic acid (0.688 g, 3.62 mmol). The resulting mixture was heated at 110°C for 3 h and was allowed to cool down. The mixture was diluted with EtOAc and washed with

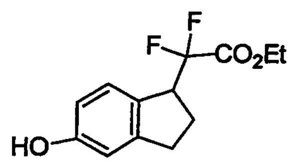
saturated sodium bicarbonate, brine and dried over Na_2SO_4. Solvent was evaporated and the residue was purified by chromatography on SiO_2, eluting with Hexanes/EtOAc (4:1) mixture to produce a desired product (3.2 g, 66%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.50 (d, 1 H), 7.06 (s, 1 H), 6.88 (d, 1 H), 6.77 (m, 1 H), 4.32 (q, 2 H), 3.83 (s, 3 H), 3.46 (d, 2 H), 1.32 (t, 3 H).

[153] Step 3. Preparation of ethyl difluoro(5-methoxy-2,3-dihydro-1*H*-inden-1-yl)acetate



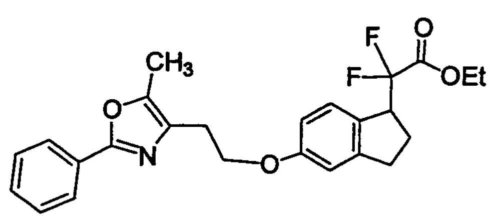
[154] The product obtained in Step 2 was hydrogenated using the procedure described for Intermediate D, Step 2. Yield: 0.70 g, 93%; ^{1}H NMR ($CDCl_3$) δ 7.22 (d, 1 H), 6.78 (s, 1 H), 6.74 (d, 1 H), 4.31 (q, 2 H), 3.87 (m, 1 H), 3.79 (s, 3 H), 3.02 (m, 1 H), 2.86 (m, 1 H), 2.87 (q, 2 H), 1.29 (t, 3 H).

[155] Step 4. Preparation of ethyl difluoro(5-hydroxy-2,3-dihydro-1*H*-inden-1-yl)acetate



[156] To a solution of $AlCl_3$ (595 mg, 4.47 mmol) in CH_2Cl_2 (2 mL), was added the product of Step 3 (402 mg, 1.49 mmol) in CH_2Cl_2 (4 mL). The mixture was cooled to 0°C for 5 minutes, then EtSH (0.330 mL, 4.47 mmol) was added slowly. The mixture was stirred at this temperature for 2 h. The mixture was then poured over ice water, stirred for 10 minutes, and extracted with CH_2Cl_2 twice. The combined organic layers were washed with water, dried over sodium sulfate, and concentrated to give product (0.10 g, 26 %). ^{1}H NMR ($CDCl_3$): δ 7.16 (d, 1 H), 6.70 (s, 1 h), 6.64 (d, 1 H), 5.04 (s, 1 H), 4.30 (q, 1 H), 3.83 (m, 1 H), 2.94 (m, 1 H), 2.81 (m, 1 H), 2.26 (q, 2 H), 1.28 (t, 3 H).

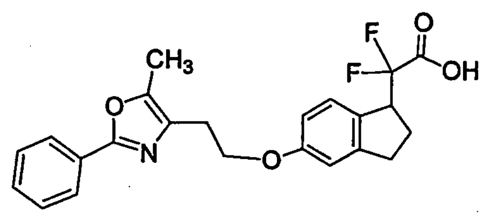
[157] Step 5. Preparation of ethyl difluoro{5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate



[158] A suspension of the hydroxyindane carboxylate prepared in Step 4 (0.064 g, 0.25 mmol), oxazole alcohol (0.067 g, 0.33 mmol, commercially available), ADDP (0.083 g, 0.25 mol), and Ph_3P (0.087 g, 0.33 mol) in 2 mL anhydrous methylene chloride was stirred at rt under argon for 24 h. The reaction mixture was diluted with MeOH (1 mL) and purified by Prep TLC eluting with Hex/EtOAc (3:1) to produce 0.089 g (81%) of the desired product. ^1H NMR ($CDCl_3$) δ 7.96 (d, 2H), 7.43 (m, 3H), 7.20 (d, 1H), 6.76 (m, 2H), 4.30 (q, 2H), 4.21 (t, 2H), 3.84 (m, 1H), 2.91 (m, 4H), 2.37 (s, 3H), 2.26 (m, 2H), 1.28 (t, 3H).

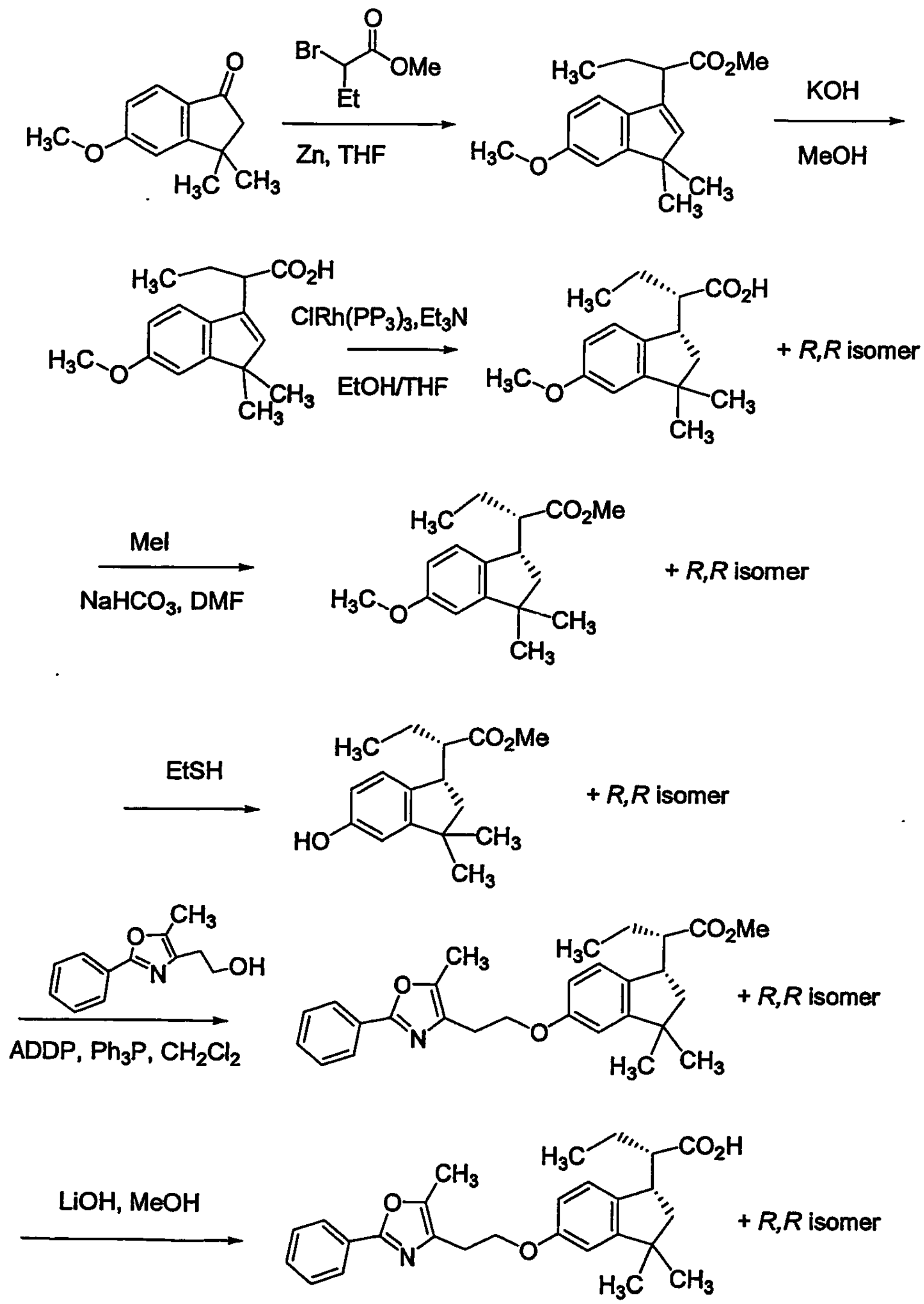
[159] **Example 13**

Preparation of difluoro{5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic acid



[160] Hydrolysis of the product of Example 12, Step 5 by the method described above for Example 2 produced 25 mg of the desired product. ^1H NMR (CD_3OD): δ 7.95 (m, 2H), 7.47 (m, 3H), 7.24 (s, 1 H), 6.77 (m, 1H), 6.69 (m, 1H), 4.20 (t, 2H), 3.84 (s, 1 H), 2.98 (m, 1H), 2.95 (t, 2H), 2.79 (m, 1H), 2.37 (s, 3H), 2.22 (m, 2H).

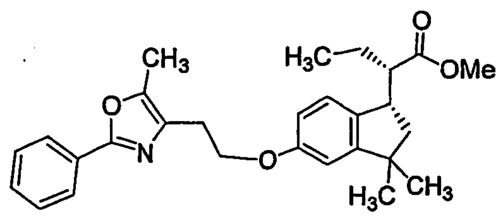
[161] Reaction Scheme 7



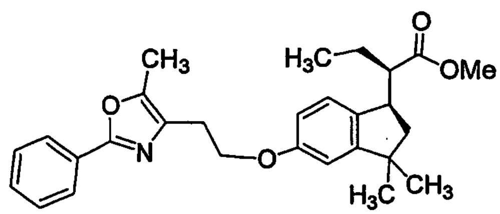
[162] Using the appropriate starting materials, Examples 14-16 were prepared by the method exemplified in Reaction Scheme 7.

[163] **Example 14**

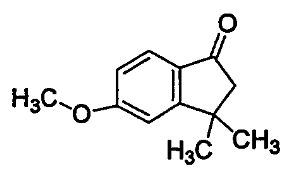
Preparation of methyl (2*S*)-2-{(1*S*)-3,3-dimethyl-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}butanoate and methyl (2*R*)-2-{(1*R*)-3,3-dimethyl-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}butanoate)



and

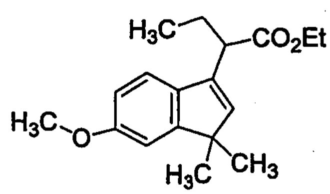


[164] Step 1. Preparation of 5-methoxy-3,3-dimethyl-1-indanone



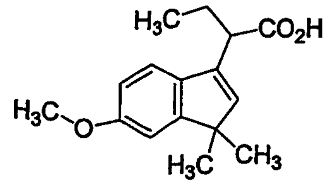
[165] The above intermediate was prepared from 6-methoxy-1,1-dimethylindane as described in Tetrahedron Lett., (41:10353-10356, 2000). LC-MS, RT 2.78 min, (M+1) 191; ^{1}H NMR ($CDCl_3$): δ 7.64 (d, 1 H), 6.88 (m, 2 H), 3.90 (s, 3 H), 2.56 (s, 2 H), 1.40 (s, 6 H).

[166] Step 2. Preparation of ethyl 2-(6-methoxy-1,1-dimethyl-1*H*-inden-3-yl)butanoate



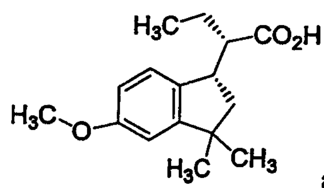
[167] The α-ethyl ester was prepared by using the procedure described for Step 1, Example 12 using ethyl bromobutyrate and the above product of Step 1 as starting materials. LC-MS, RT 3.68 min, (M+1) 289; ^{1}H NMR ($CDCl_3$): δ 7.25 (d, 1 H), 6.88 (d, 1 H), 6.76 (d, 1 H), 6.10 (s, 1 H), 4.15 (q, 2 H), 3.82 (s, 3 H), 3.46 (m, 1 H), 2.02 (m, 1 H), 1.89 (m, 1 H), 1.27 (d, 6 H), 1.21 (t, 3 H), 0.96 (t, 3 H).

[168] Step 3. Preparation of 2-(6-methoxy-1,1-dimethyl-1*H*-inden-3-yl)butanoic acid

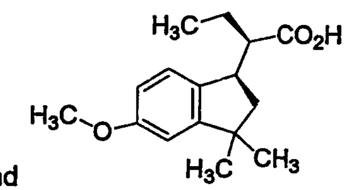


[169] Hydrolysis of the product of Step 2 by the method described for Example 2 produced 280 mg of the desired product. LC-MS, RT 3.11 min, (M+1) 261; ^{1}H NMR ($CDCl_3$): δ 7.24 (s, 1 H), 6.86 (d, 1 H), 6.75 (dd, 1 H), 6.13 (s, 1 H), 3.81 (s, 3 H), 3.48 (t, 1 H), 2.03 (m, 1 H), 1.88 (m, 1 H), 1.27 (s, 6 H), 0.96 (t, 3 H).

[170] Step 4. Preparation of (2*S*)-2-[(1*S*)-5-methoxy-3,3-dimethyl-2,3-dihydro-1*H*-inden-1-yl]butanoic acid and (2*R*)-2-[(1*R*)-5-methoxy-3,3-dimethyl-2,3-dihydro-1*H*-inden-1-yl]butanoic acid

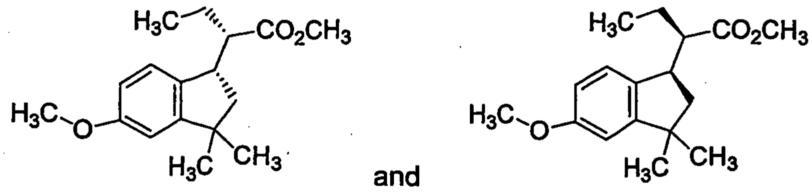


and



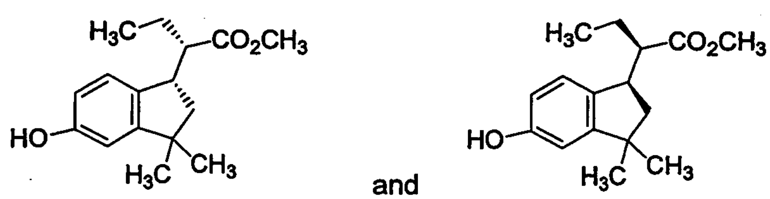
[171] A solution of the product obtained in Step 3 (0.270 g, 1.04 mmol), $ClRh(PPh_3)_3$ (0.050 g, 5% eq.), and triethylamine (0.158 g, 1.56 mmol) in EtOH (27 mL) and THF (3 mL) was shaken in a pressure bottle under 60 psi H_2 for 16 h. The solvents were removed at a reduced pressure. The resulting mixture was stirred in a solution of 15 mL of 1N HCl and 15 mL CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined CH_2Cl_2 layers were washed with 1N HCl solution and stirred with 15 mL of 1N NaOH solution. The organic layer was extracted with 1N NaOH solution. The combined aqueous layer was washed with CH_2Cl_2 (2 x 25 mL), and acidified (pH 2.0-3.0) by a slow addition of conc. HCl solution at below 15°C. The acidic mixture was extracted with CH_2Cl_2 (2 x 30 mL), and washed with water (2 x 25 mL) until pH 5.0-6.0. After washing with brine and drying over anhydrous Na_2SO_4, solvent was evaporated under a reduced pressure. The product (0.32 g, 86%) was obtained as an oil. ^{1}H NMR ($CDCl_3$): δ 7.08 (d, 1 H), 6.74 (dd, 1 H), 6.70 (d, 1 H), 3.82 (s, 3 H), 3.62 (q, 1 H), 2.68 (m, 1 H), 2.08 (m, 1 H), 1.77 (m, 1 H), 1.69 (m, 1 H), 1.52 (m, 1 H), 1.32 (s, 3 H), 1.20 (s, 3 H), 1 .01 (t, 3 H).

[172] Step 5. Preparation of methyl (2*S*)-2-[(1*S*)-5-methoxy-3,3-dimethyl-2,3-dihydro-1*H*-inden-1-yl]butanoate and methyl (2*R*)-2-[(1*R*)-5-methoxy-3,3-dimethyl-2,3-dihydro-1*H*-inden-1-yl]butanoate



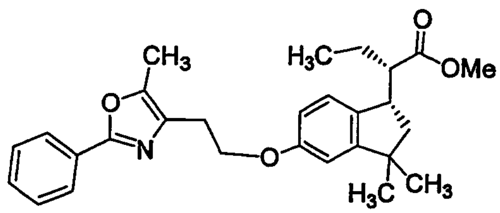
[173] A suspension of acid prepared in Step 4 (0.225 g, 0.86 mmol), $NaHCO_3$ (0.217 g, 2.58 mmol), CH_3I (0.183 g, 1.29 mmol) in 3 mL DMF was stirred under Ar for 18 h. NMR analysis showed the reaction to be 95% complete. Adding 0.137 g CH_3I, and stirring for an additional 24 h at rt for the reaction to reach completion. The reaction mixture was poured into 20 mL water, and extracted with EtOAc (2 x20 mL). The organic layer was sequentially washed with water (2 x 50 mL), 50 mL of 1N NaOH solution, water (2 x 50 mL), and brine, and dried over Na_2SO_4. Volatiles were evaporated to give a desired product. Yield: 0.22 g, 93 %; ^1H NMR ($CDCl_3$): δ 6.91 (d, 1 H), 6.70 (d, 1 H), 6.68 (dd, 1 H), 3.80 (s, 3 H), 3.76 (s, 3 H), 3.50 (q, 1 H), 2.56 (m, 1 H), 2.02 (m, 1 H), 1.72 (m, 1 h), 1.64 (m, 1 H), 1.49 (m, 1 H), 1.34 (s, 3 H), 1.16 (s, 3 H), 0.89 (t, 3 H).

[174] Step 6. Preparation of methyl (2*S*)-2-[(1*S*)-5-hydroxy-3,3-dimethyl-2,3-dihydro-1*H*-inden-1-yl]butanoate and methyl (2*R*)-2-[(1*R*)-5-hydroxy-3,3-dimethyl-2,3-dihydro-1*H*-inden-1-yl]butanoate

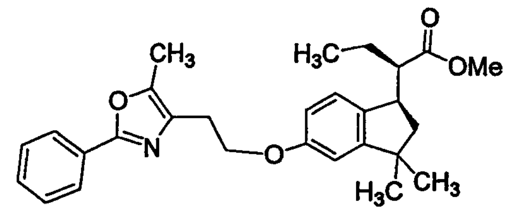


[175] The intermediate was prepared by using the procedure described in Example 12, Step 4. ^1H NMR ($CDCl_3$): δ 6.83 (d, 1 H), 6.61 (m, 2 H), 5.19 (s, 1 H), 3.77 (s, 3 H), 3.49 (q, 1 H), 2.56 (m, 1 H), 2.01 (m, 1 H), 1.70 (m, 1 H), 1.64 (m, 1 H), 1.51 (m, 1 H), 1.31 (s, 3 H), 1.15 (s, 3 H), 0.91 (t, 3 H).

[176] Step 7. Preparation of methyl (2*S*)-2-{(1*S*)-3,3-dimethyl-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}butanoate and methyl (2*R*)-2-{(1*R*)-3,3-dimethyl-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}butanoate



and



[177] The coupling of the hydroxy indane acetic acid ester of Step 6 with oxazole alcohol using the procedure of Example 12, Step 5 produced 0.047 g (32%) of the desired product. ^{1}H NMR (CD_3OD): δ 7.93 (m, 2 H), 7.44 (m, 3 H), 6.84 (d, 1 H), 6.68 (m, 2 H), 4.21 (t, 2 H), 3.72 (s, 3 H), 3.41 (q, 1 H), 2.94 (t, 2 H), 2.50 (m, 1 H), 2.35 (s, 3 H), 1.97 (dd, 1 H), 1.66 (dd, 1 H), 1.58 (m, 1 H),1.48 (m, 1 H), 1.28 (t, 3 H), 1.10 (t, 3 H), 0.87 (t, 3 H).

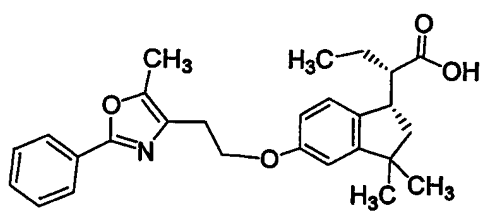
[178]

Example 15

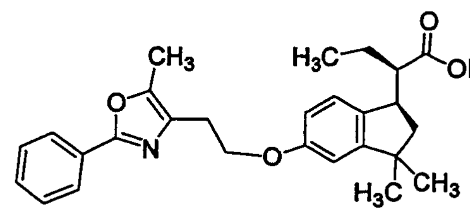
Preparation of (2*S*)-2-{(1*S*)-3,3-dimethyl-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}butanoic acid

and

(2*R*)-2-{(1*R*)-3,3-dimethyl-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}butanoic acid



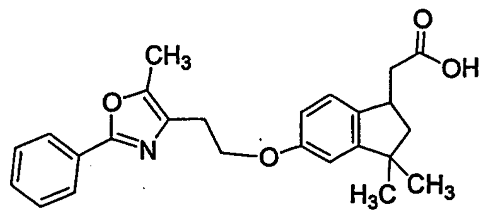
and



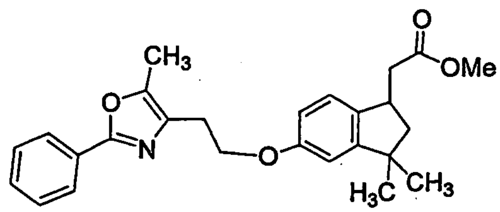
[179] Hydrolysis of the products of Example 14 using the method described above for Example 2 produced 25 mg of the desired product. LC-MS, RT 3.55 min, (M+1) 433; ^{1}H NMR ($CDCl_3$): δ 7.94 (m, 2H), 7.45 (m, 3H), 7.01 (d, 1 H), 6.68 (m, 2 H), 4.21 (t, 2 H), 3.44 (q, 1 H), 2.95 (t, 2 H), 2.46 (m, 1 H), 2.36 (s, 3 H), 1.99 (dd, 1 H), 1.66 (dd, 1 H), 1.57 (m, 1 H), 1.47 (m, 1 H), 1.29 (s, 3 H), 1.11 (s, 3 H), 0.92 (t, 3 H).

[180] Example 16

Preparation of {3,3-dimethyl-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic acid

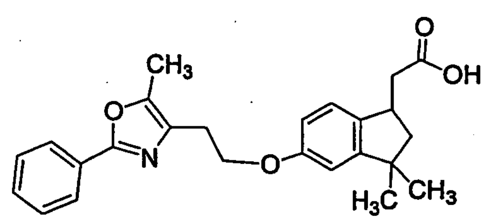


[181] Step 1. Preparation of methyl {3,3-dimethyl-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate



[182] The title compound was prepared using the procedure described for Intermediate D, Steps 1, 2 and 6, and using ethyl bromoacetate and the starting ketone of Example 14 as starting materials and using the coupling method of Example 14, Step 7. Yield: 0.15 g, 54%. LC-MS, RT 4.54 min, (M+1) 420; ^{1}H NMR ($CDCl_3$): δ 7.91 (m, 2H), 7.41 (m, 3H), 6.95 (s, 1H), 6.66 (m, 2H), 4.18 (t, 2H), 3.67 (s, 3 H), 3.45 (m, 1 H), 2.91 (t, 2H), 2.78 (dd, 1H), 2.32 (s, 3 H), 2.29(dd, 1H), 2.14 (dd, 1H), 1.50 (m, 1H), 1.25 (s, 3H), 1.09 (s, 3H).

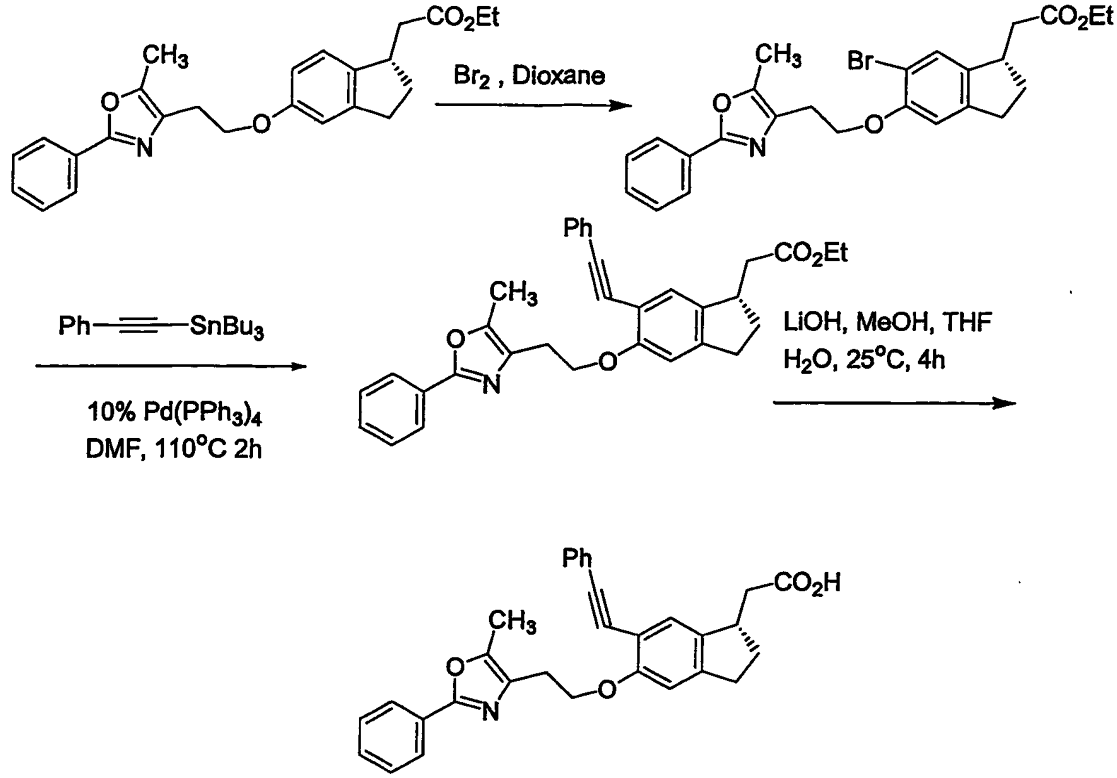
[183] Step 2. Preparation of {3,3-dimethyl-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic acid



[184] Hydrolysis of the product of Step 1 by the method described in Example 2 produced 0.08 g, (61%) of the desired product. LC-MS, RT 3.20 min, (M+1) 406; ^{1}H NMR (CD_3OD): δ 7.93 (m, 2H), 7.43 (m, 3H), 7.01 (d, 1H), 6.68 (m, 2H), 4.20 (t, 2H), 3.47 (m, 1H), 2.93 (s, 2H), 2.78 (dd, 1 H), 2.35 (s, 3H), 2.29 (dd, 1H), 2.20 (dd, 1H), 1.54 (dd, 1H), 1.22 (s, 3H), 1.12 (s, 3H).

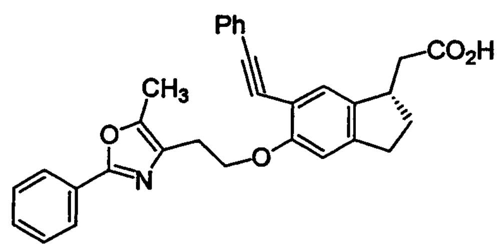
[185] Reaction Scheme 8 summarizes the steps for the preparation of Example 17.

[186] **Reaction Scheme 8**

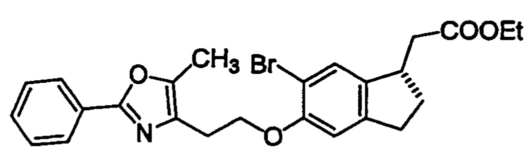


[187] **Example 17**

Preparation of [(1*S*)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-6-(phenylethynyl)-2,3-dihydro-1*H*-inden-1-yl]acetic acid



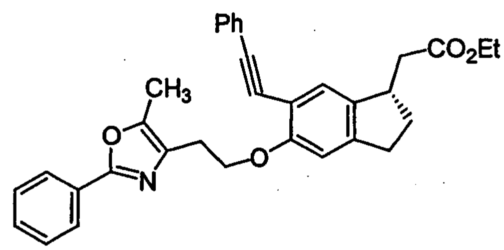
[188] Step 1: Preparation of ethyl {(1*S*)-6-bromo-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate



[189] To a solution of bromine (0.02 mL, 0.44 mmol) in 5 mL dioxane was added ethyl {(1*S*)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}acetate (170 mg, 0.419 mmol), prepared using Intermediate D and 2-(5-methyl-2-phenyl-1,3-

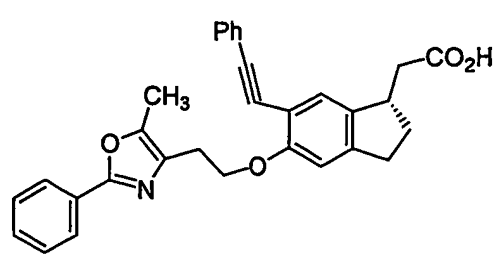
oxazol-4-yl)-1-ethanol, and using the method described for Example 12, Step 5. The reaction was stirred at rt until TLC showed consumption of starting material. The reaction mixture was then diluted with ethyl ether and washed one time with saturated, aqueous sodium bicarbonate. The aqueous wash was separated and then extracted with ether. The organic phases were combined, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography (30% ethyl acetate in hexane) to provide the desired product (130 mg, 64%).

[190] Step 2: Preparation of ethyl [(1*S*)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-6-(phenylethynyl)-2,3-dihydro-1*H*-inden-1-yl]acetate



[191] Argon was bubbled through a solution of the product of Step 1 (142 mg, 0.29 mmol), $Pd(PPh_3)_4$ (35 mg, 0.03 mmol), and tributyl(phenylethynyl)tin (227 mg, 0.58 mmol) in 1.45 mL DMF. After 20 minutes, the reaction mixture was heated to 130°C for 18 h. At this time, it was cooled to rt, quenched with saturated aqueous potassium fluoride, and extracted two times with dichloromethane. The organic extracts were combined, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (25% ethyl acetate in hexanes) to provide the desired product (40.8 mg, 28%). ES-MS *m/z* 506.2 $(M+H)^+$; HPLC RT 4.66; ^1H NMR ($CDCl_3$): δ 0.87 (t, 3H), 1.70-1.79 (m, 1H), 2.33 (s, 3H), 2.36-2.42 (m, 2H), 2.68-2.75 (m, 1H), 2.85 (q, 2H), 3.04 (t, 2H), 3.51 (m, 1H), 4.07-4.20 (q, 2H), 4.31 (t, 2H), 6.80 (s, 1H), 7.25-7.52 (m, 9H), 7.93-7.97 (m, 2H).

[192] Step 3: Preparation of [(1*S*)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-6-(phenylethynyl)-2,3-dihydro-1*H*-inden-1-yl]acetic acid



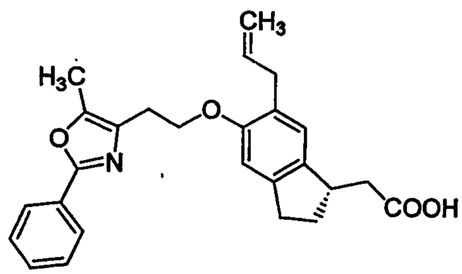
[193] Lithium hydroxide (1.4 mg, 0.06 mmol) was added to a solution of the product of Step 2 (11.2 mg 0.02 mmol) in 0.2 mL of a mixture of water, THF, and EtOH (1:1:1). The

reaction mixture was stirred at rt for 18 h. It was then quenched with 1N aqueous HCl, diluted with water, and extracted two times with ethyl ether. The organic extracts were combined, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to provide the desired product as a pale yellow solid (10.4 mg, quant.). ES-MS *m/z* 478.5 $(M+H)^+$; HPLC RT 3.71; ^{1}H NMR ($CDCl_3$: δ 1.75 (m, 1H), 2.34 (s, 3H), 2.37-2.48 (m, 2H), 2.76-2.89 (m, 3H), 3.05 (t, 2H), 3.50 (m, 1H), 4.32 (t, 2H), 6.80 (s, 1H), 7.30 (m, 4H), 7.40 (m, 2H), 7.49 (m, 3H), 7.97 (m, 2H).

[194] The following compound was prepared using a similar procedure to that of Example 17.

[195] **Example 18**

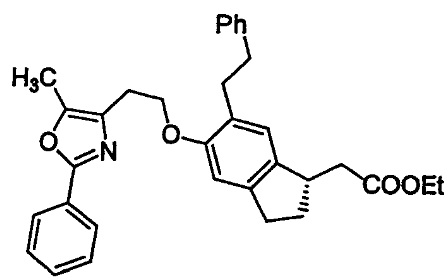
Preparation of {(1*S*)-6-allyl-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic acid



[196] ES-MS *m/z* 418.6 ($(M+H)^+$); HPLC RT 3.50.

[197] **Example 19**

Preparation of ethyl [(1*S*)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-6-(2-phenylethyl)-2,3-dihydro-1*H*-inden-1-yl]acetate

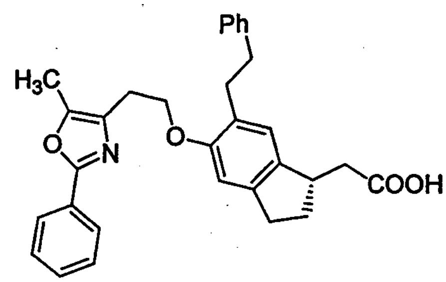


[198] A round bottom flask charged with 3.8 mg of 10% palladium on carbon was evacuated and flushed with argon. The palladium on carbon was then wet with a minimal amount of ethanol, and a solution of the product from Step 2, Example 17 (38 mg, 0.075 mmol) dissolved in ethanol was added. The flask was then evacuated and back-filled with argon again. A third evacuation under argon was performed and then the flask was opened up to a hydrogen filled balloon at atmospheric pressure. The reaction was stirred

at rt for 18 h, then filtered through Celite®. The resulting solution was concentrated and purified by preparative TLC using (25% ethyl acetate in hexane) to provide the desired product (15.4 mg, 40%). ES-MS m/z 510.6 $(M+H)^+$; HPLC RT 4.45; ^1H NMR ($CDCl_3$): δ 1.19 (t, 3H), 1.61-1.69 (m, 1H), 2.23 (s, 3H), 2.30 (m, 2H), 2.57-2.64 (m, 1H), 2.74 (m, 4H), 2.91 (t, 2H), 3.41 (m, 1H), 4.09 (m, 4H), 4.18 (t, 2H), 6.70 (s, 1H), 6.81 (s, 1H), 7.06-7.21 (m, 5H), 7.34 (m, 3H), 7.89 (m, 2H).

[199] **Example 20**

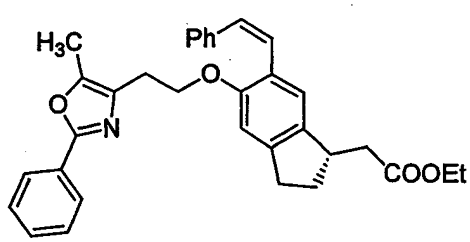
Preparation of [(1*S*)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-6-(2-phenylethyl)-2,3-dihydro-1*H*-inden-1-yl]acetic acid



[200] The ester (14 mg, 0.028 mmol) of Example 19, was dissolved in 0.3 mL of a 1:1:1 solution of water, tetrahydrofuran, and ethanol. Lithium hydroxide (1.9 mg, 0.078 mmol) was then added and the resulting mixture was stirred at rt for 18 h. The reaction was then diluted with water, acidified with 1N HCl, and extracted twice with diethyl ether. The organic extracts were combined, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to provide the acid (11.3 mg, 90%) as a white solid. ES-MS m/z 482.6 $(M+H)^+$; HPLC RT 3.80.

[201] **Example 21**

Preparation of ethyl {(1*S*)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-6-[(*Z*)-2-phenylethenyl]-2,3-dihydro-1*H*-inden-1-yl}acetate

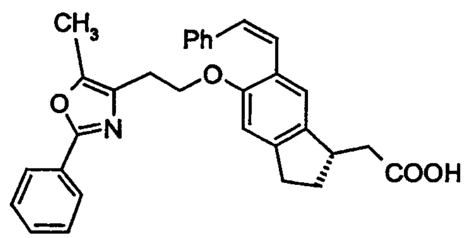


[202] A round bottom flask charged with 2.4 mg of Lindlar Catalyst was evacuated and back-filled with argon. The catalyst was wet with a minimal amount of ethanol, and an ethanol solution of the product from Step 2, Example 17 (24 mg, 0.05 mmol) was added in ethanol. The flask was evacuated and back-filled with argon again. Another

evacuation under vacuum was performed and then the flask was opened up to a hydrogen filled balloon. The reaction was stirred at rt for 18 h, then filtered through Celite®. The resulting solution was concentrated and then purified by preparative TLC using 25%ethyl acetate in hexane to provide the desired product (14 mg, 55%). ES-MS *m/z* 508.6 $(M+H)^+$; HPLC RT 4.54; ^1H NMR ($CDCl_3$): δ 1.20 (t, 3H), 1.66 (m, 2H), 2.20 (m, 1H), 2.36 (s, 3H), 2.39-2.46 (m, 1H), 2.85 (m, 2H), 2.90 (t, 2H), 3.35 (m, 1H), 4.00-4.08 (q, 2H), 4.21 (t, 2H), 6.49-6.63 (dd, 2H), 6.78 (s, 1H), 6.97 (s, 1H), 7.14-7.26 (m, 5H), 7.40 (m, 3H), 7.95 (m, 2H).

[203] **Example 22**

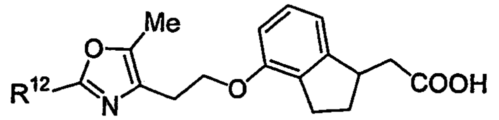
Preparation of {(1*S*)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-6-[(Z)-2-phenyl-ethenyl]-2,3-dihydro-1*H*-inden-1-yl}acetic acid

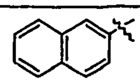


[204] The ester of Example 21 was dissolved in 0.3 mL of a 1:1:1 solution of water, tetrahydrofuran, and ethanol. Lithium hydroxide (2 mg, 0.084 mmol) was then added and the resulting mixture was stirred at rt for 48 h. The reaction was then diluted with water, acidified with 1N HCl, and extracted twice with diethyl ether. The organic extracts were combined, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to provide the acid (11.4 mg, 85%) as a white solid. ES-MS *m/z* 480.5 ($(M+H)^+$); HPLC RT 3.85.

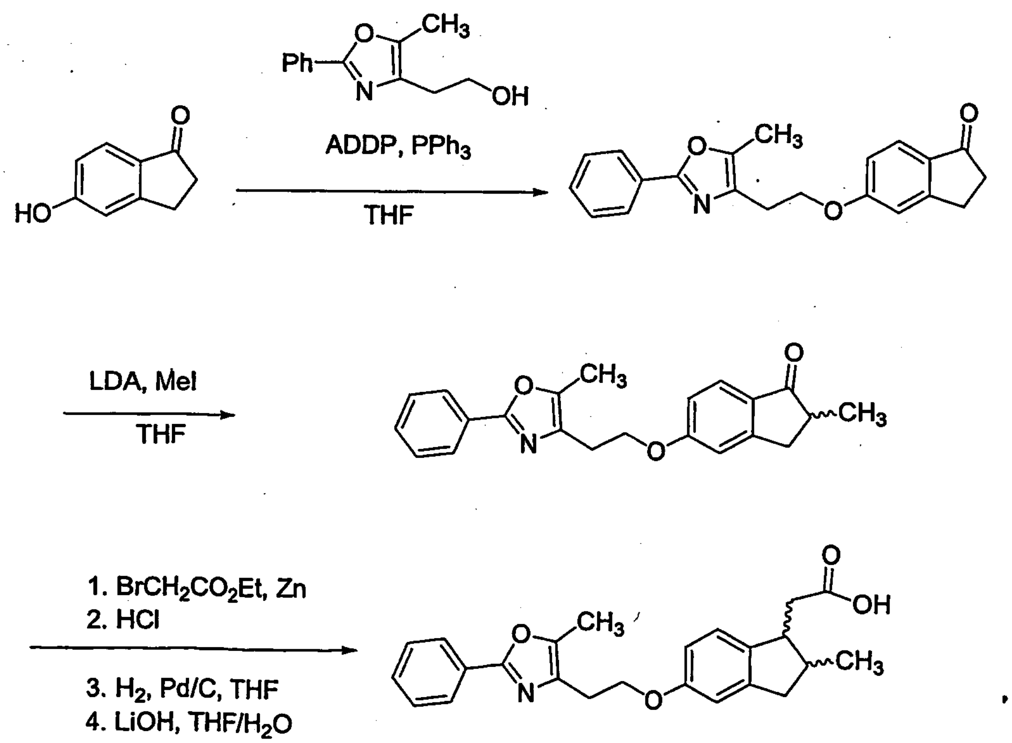
[205] By using 4-methoxy-1-indanone as starting material instead of 5-methoxy-1-indanone, the following regioisomeric compounds were prepared by methods similar to those used for preparation of Intermediates A-F; Example 12, Step 5; and Example 13 described above.

[206] **Table 2**



Example No.	R^{12}	LC-MS $[M+H]^+$	IUPAC Name
23		428.2	(4-{2-[5-methyl-2-(2-naphthyl)-1,3-oxazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid
24	Ph	378.1	{4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic acid
25	4-F-Ph	396.1	(4-{2-[2-(4-fluorophenyl)-5-methyl-1,3-oxazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid
26	3-Me-4-F-Ph	410.2	(4-{2-[2-(4-fluoro-3-methylphenyl)-5-methyl-1,3-oxazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid

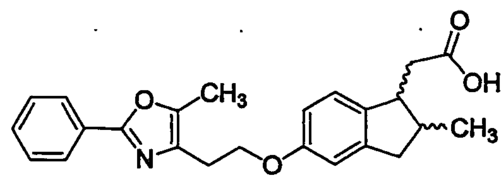
[207] **Reaction Scheme 9**



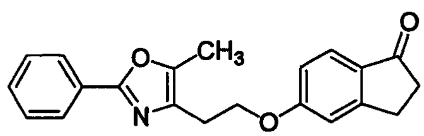
[208] Using the appropriate starting materials, Example 27 was prepared by the method exemplified in Reaction Scheme 9.

[209] **Example 27**

Preparation of {2-methyl-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}acetic acid

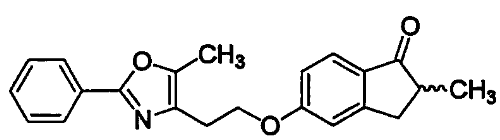


[210] Step 1. 5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-1-indanone



[211] A suspension of 5-hydroxy-1-indanone (936 mg, 6 mmol, commercially available), 2-(5-methyl-2-phenyloxazol-4-yl)ethanol (1220 mg, 6 mmol, commercially available), ADDP (3028 mg, 12 mmol), and Ph_3P (3148 mg, 12 mmol) in 15 mL anhydrous CH_2Cl_2 was stirred at rt under argon for 48 h. Purification by column chromatography (25% EtOAc/hexane) gave 1320 mg (83%) of the product, a white solid. LC/MS retention time 3.11 min; MS (ES) [M+1] 334.2 ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H), 2.65-2.72 (m, 2H), 3.05-3.18 (m, 4H), 4.35 (t, 2H,), 6.95 (d, 2H), 7.53-7.58 (m, 3H), 7.70 (d, 1H), 7.89-8.05 (m, 2H).

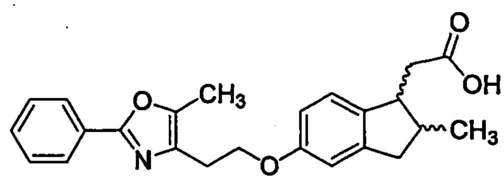
[212] Step 2. 2-methyl-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-1-indanone



[213] To a solution of LDA (1.47 mL of a 2M solution, 2.95 mmol) in THF (17 mL) at –78°C was added dropwise by syringe a solution of 5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-1-indanone (992 mg, 2.98 mmol) in THF (3 mL). The resulting mixture was stirred at –78°C for 1 h after which methyl iodide (0.2 mL, 3.12 mmol) was added dropwise. The mixture was stirred for an additional 1 h at –78°C and then allowed to warm to rt. The reaction mixture was then quenched with a 15% solution of HCl (10 mL) and extracted with EtOAc (3 x 10 mL). The organic extract was washed with brine, dried over sodium sulfate, after which the solvent was removed under reduced pressure. The residue was purified by flash column chromatography to give 270 mg of the product

(26%) as a pale yellow solid. LC/MS retention time 3.39 min; MS (ES) [M+1] 348.1 ^{1}H NMR ($CDCl_3$): δ 1.32 (d, 3H), 2.39 (s, 3H), 2.62-2.78 (m, 2H), 3.05-3.18 (m, 2H), 3.30-3.38 (m, 1H), 4.30 (t, 2H), 6.89 (d, 2H), 7.61-7.65 (m, 3H), 7.71 (d, 1H), 7.89-8.00 (m, 2H).

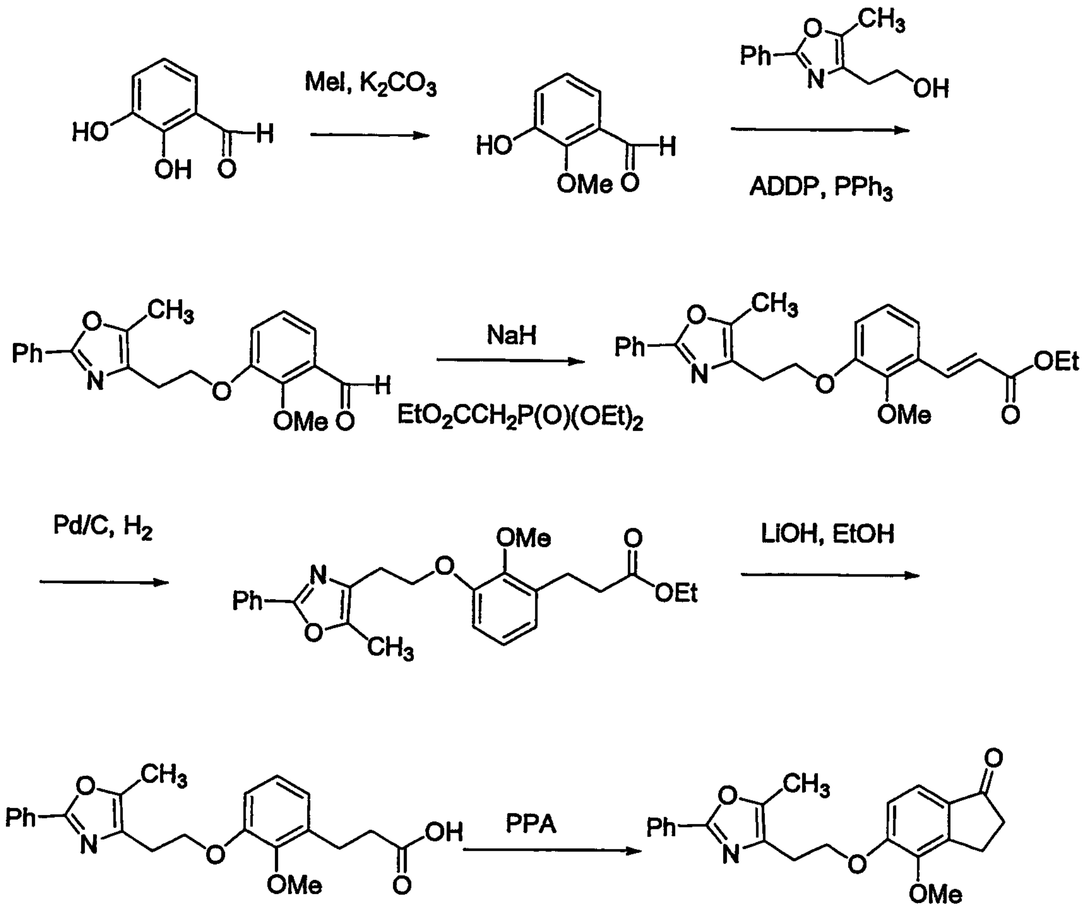
[214] Step 3. {2-methyl-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic acid



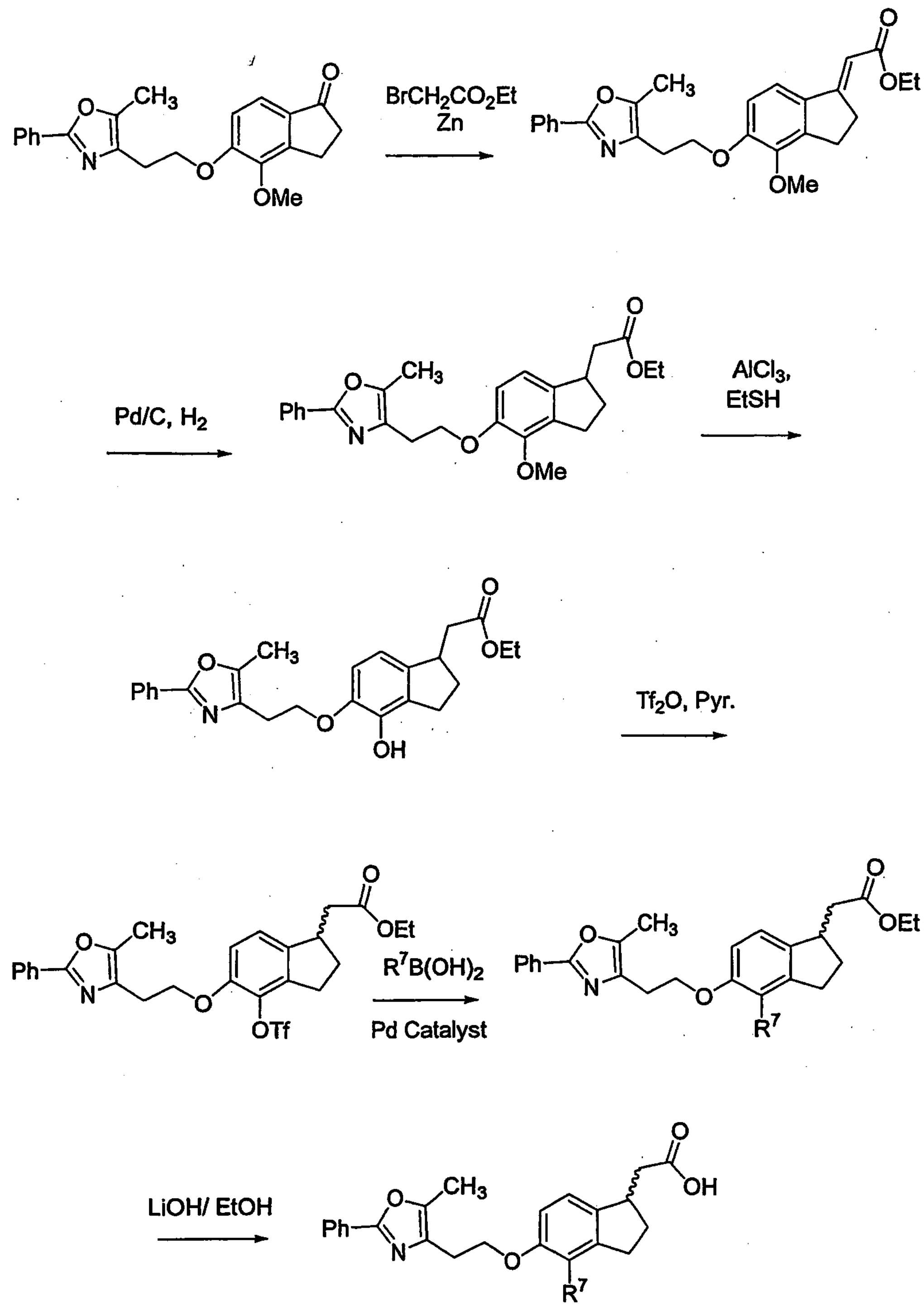
[215] To 2-methyl-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-1-indanone (220 mg, 0.63 mmol), was applied the Reformatsky procedure in Step 1 of Intermediate D. This was followed by catalytic Pd/C hydrogenation as outlined in Step 2 of Intermediate D and the standard hydrolysis conditions as described in Step 3 of Intermediate D to give 18 mg (14%) of the product as a white solid. LC/MS retention time 3.39 min; MS (ES) [M+1] 392.2 ^{1}H NMR ($CDCl_3$): δ 1.03 (d, 3H), 2.38 (s, 3H), 2.45-2.60 (m, 3H), 2.65-2.80 (m, 1H), 2.98-3.02 (m, 3H), 3.50 (q, 1H), 4.20 (t, 2H), 6.70 (d, 1H), 6.78 (d, 1H), 7.08 (d, 1H), 7.61-7.65 (m, 3H), 7.89-8.00 (m, 2H).

[216] Using the appropriate starting materials, Example 28-44 were prepared by the methods exemplified in Reaction Scheme 10, parts 1 and 2.

[217] **Reaction Scheme 10, Part 1**

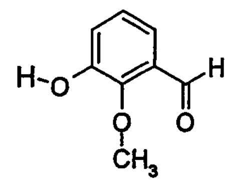


[218] **Reaction Scheme 10, Part 2**



[219] **Example 28**

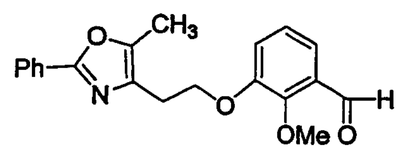
Preparation of 3-Hydroxy-2-methoxybenzaldehyde



[220] A solution of 2,3-dihydroxybenzaldehyde (10 g, 72 mmol) in anhydrous DMF (100 mL) was treated with K_2CO_3 (10 g, 72 mmol) at 25°C and the mixture was stirred for 30 minutes. Iodomethane (4.9 mL, 80 mmol) was added and the reaction was further stirred for 20 h. The reaction was quenched with water and extracted with diethyl ether. The organic layer was dried using sodium sulfate and solvents were evaporated under vacuum. The residue was purified by Biotage to obtain 3-hydroxy-2-methoxybenzaldehyde (6.8 g, 45 mmol, 62%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 4.0 (s, 3H), 5.9 (s, 1H), 7.2 (m, 2H), 7.4 (m, 1H), 10.3 (s, 1H); GC/MS (ES) 153 $(M+1)^+$.

[221] **Example 29**

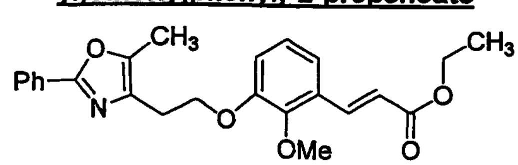
Preparation of 2-methoxy-3-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]benzaldehyde



[222] To a flask containing 3-hydroxy-2-methoxybenzaldehyde (0.2 g, 1.3 mmol), 2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethanol (0.29 g, 1.5 mmol), TMAD (0.45 g, 2.6 mmol), and triphenyphosphine (0.69 g, 2.6 mmol) was added with THF (2 mL) under argon. The reaction was stirred at rt for 72 h. The reaction mixture was filtered through a silica-gel plug and solvents were evaporated under vacuum. The residue was purified by Biotage to obtain 2-methoxy-3-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]benzaldehyde (0.2 g, 0.6 mmol) in 45% yield. ^{1}H NMR ($CDCl_3$) δ 2.4 (s, 3H), 3.1 (t, 2H), 3.9 (s, 3H), 4.3 (t, 2H), 7.2 (m, 2H), 7.4 (m, 4H), 7.9 (m, 2H), 10.4 (s, 1H); GC-MS (ES) 338 $(M+1)^+$.

[223] **Example 30**

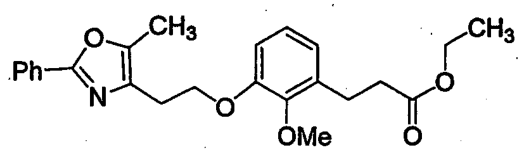
Preparation of ethyl -3-{2-methoxy-3-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]phenyl}-2-propenoate



[224] To a flask containing triethyl phosphonoacetate (5.8 mL, 29.4 mmol) in THF (20 mL) was added 60% NaH (1.2 g, 29.4 mmol), and the mixture was stirred for 1 h. 2-Methoxy-3-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]benzaldehyde (7.6 g, 22.6 mmol) in THF (15 mL) was added to the reaction mixture, and the mixture was heated at 65°C for 20 h. The reaction was quenched with water and the aqueous layer was extracted with diethyl ether. Solvents were evaporated under vacuum and the residue was purified by Biotage to obtain the desired product (8.2 g, 20.1 mmol) in 89% yield. ^{1}H NMR ($CDCl_3$) δ 1.3 (t, 3H), 2.4 (s, 3H), 3.0 (t, 2H), 3.8 (s, 3H), 4.3 (m, 4H), 6.4 (d, 1H), 7.0 (m, 2H), 7.2 (m, 1H), 7.4 (m, 3H), 7.9 (m, 3H); GC-MS (ES) 408 $(M+1)^+$.

[225] **Example 31**

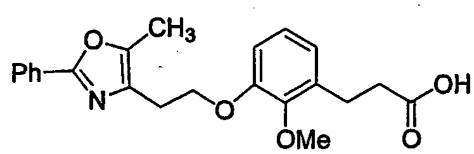
Preparation of ethyl 3-{2-methoxy-3-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]phenyl}propanoate



[226] To a flame dried flask under argon was added Pd/C (10%, 0.56 g) and ethanol (10 mL) to wet the palladium. A solution of ethyl-3-{2-methoxy-3-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]phenyl}-2-propenoate (5.6 g, 13.7 mmol) in ethanol was added slowly to the flask containing Pd/C under argon. A hydrogen balloon was connected to the flask and the mixture was stirred under hydrogen for 16 h. The reaction was filtered through a Celite® plug and the filtrate was evaporated under vacuum. The residue was purified by Biotage to obtain the desired product (5.6 g, 13.6 mmol) as a solid in > 99% yield. ^{1}H NMR ($CDCl_3$) δ 1.2 (t, 3H), 2.4 (s, 3H), 2.6 (t, 2H), 2.9 (t, 2H), 3.0 (t, 2H), 3.8 (s, 3H), 4.1 (q, 2H), 4.3 (t, 2H), 6.8 (m, 2H), 6.9 (t, 1H), 7.4 (m, 3H), 7.9 (m, 2H); MS (ES) 410 $(M+1)^+$.

[227] **Example 32**

Preparation of 3-{2-methoxy-3-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]phenyl}propanoic acid

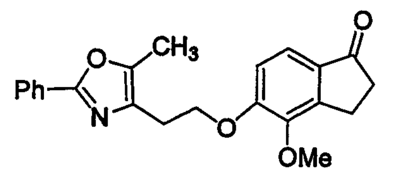


[228] Ethyl 3-{2-methoxy-3-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]phenyl}propanoate (5.5 g, 13.4 mmol) was dissolved in EtOH (25 mL) and $LiOH.H_2O$ (1.6 g, 67 mmol) was added. Water (25 mL) was added, and THF was added until the cloudy solution became clear. The resulting mixture was stirred overnight at rt.

HCl (2N) was added to adjust the pH to 5, then extracted three times with ethyl acetate. The solvents were evaporated to obtain the title compound (4.7 g, 12.3 mmol) in 92% yield. ^{1}H NMR ($CDCl_3$) δ 2.4 (s, 3H), 2.7 (t, 2H), 2.9 (t, 2H), 3.0 (t, 2H), 3.8 (s, 3H), 4.3 (t, 2H), 6.8 (m, 2H), 6.9 (t, 1H), 7.4 (m, 3H), 7.9 (m, 2H); MS (ES) 382 $(M+1)^+$.

[229] **Example 33**

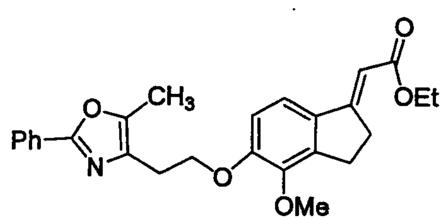
Preparation of 4-methoxy-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-1-indanone



[230] To a flask containing 3-{2-methoxy-3-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]phenyl}propanoic acid (4.5 g, 11.8 mmol) was added polyphosphoric acid (45 g), and the mixture was heated to 80°C for 3 h. The reaction was cooled down to rt, diluted with water, and poured into 1N NaOH aqueous solution. The aqueous layer was extracted with diethyl ether and dried with sodium sulfate. Solvents were evaporated under vacuum to obtain the title compound (3.8 g, 10.3 mmol) in 87% yield. ^{1}H NMR ($CDCl_3$) δ 2.4 (s, 3H), 2.7 (t, 2H), 3.0 (m, 4H), 3.8 (s, 3H), 4.4 (t, 2H), 7.0 (d, 1H), 7.4 (m, 4H), 8.0 (m, 2H); MS (ES) 364 $(M+1)^+$.

[231] **Example 34**

Preparation of Ethyl (2E)-{4-methoxy-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-ylidene}ethanoate

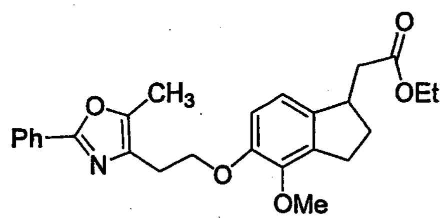


[232] To a solution of 4-methoxy-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-1-indanone (3.5 g, 9.6 mmol) in toluene/THF (50:1, 50 mL) was added Zn powder (1.1 g, 16.8 mmol) and CuCl (0.2 g, 1.9 mmol). The reaction was stirred for 30 minutes at 90°C. The reaction was removed from the oil bath and ethyl bromoacetate (1.6 mL, 14.5 mmol) was added, and then stirred at 100°C for 4 h. The reaction was cooled to rt and diluted with ether and extracted with 2N HCl. The organic layer was dried with sodium sulfate and solvents were evaporated under vacuum. The residue was purified by Biotage to obtain the desired product (1 g, 2.3 mmol) in 23% yield. ^{1}H NMR ($CDCl_3$) δ 1.3 (t, 3H),

2.5 (s, 3H), 3.0 (t, 2H), 3.1 (m, 2H), 3.3 (m, 2H),3.8 (s, 3H), 4.2 (q, 2H), 4.3 (t, 2H), 6.2 (s, 1H), 6.9 (d, 1H), 7.3 (d, 1H), 7.5 (m, 3H), 8.0 (m, 2H); MS (ES) 434 $(M+1)^+$.

[233] **Example 35**

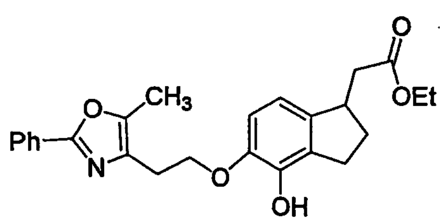
Preparation of ethyl {4-methoxy-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate



[234] To a flame dried flask under argon was added 10% Pd/C (10% w/w, 0.06 g) and ethanol (2 mL) to wet the palladium. A solution of ethyl-{4-methoxy-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-ylidene}ethanoate (0.6 g, 1.4 mmol) in ethanol was added slowly to the flask containing Pd/C under argon. A hydrogen balloon was connected to the flask and the mixture was stirred under hydrogen for 16 h. The reaction was filtered through a Celite® plug and the filtrate was evaporated under vacuum. The residue was purified by Biotage to obtain the desired product (0.52 g, 1.2 mmol) in 86% yield. ^1H NMR ($CDCl_3$) δ 1.3 (t, 3H), 1.7 (m, 1H), 2.5 (m, 5H), 2.8 (m, 3H), 3.1 (t, 2H), 3.5 (m, 1H), 3.8 (s, 3H), 4.1 (q, 2H), 4.3 (t, 2H), 6.8 (m, 2H), 7.5 (m, 3H), 8.0 (m, 2H); MS (ES) 436 $(M+1)^+$.

[235] **Example 36**

Preparation of ethyl {4-hydroxy-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate

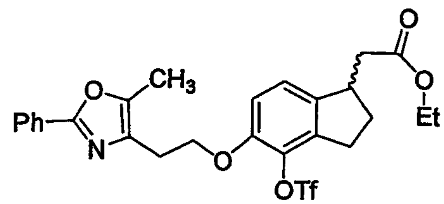


[236] A solution of ethyl {4-methoxy-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate (0.48 g, 1.1 mmol) in dichloromethane (15 mL) was cooled to 0°C, and aluminum chloride (0.74 g, 5.5 mmol) was added. The reaction was stirred for 5 minutes, and ethane thiol (0.4 mL, 5.5 mmol) was added. The reaction was stirred for 1 h and poured into 50 g ice water. The aqueous layer was extracted with dichloromethane. The organic layer was washed with brine and dried with sodium sulfate. Solvents were evaporated under vacuum. The residue was purified by Biotage

to obtain the title compound (0.45 g, 1.1 mmol) in 97% yield. ^{1}H NMR ($CDCl_3$) δ 1.3 (t, 3H), 1.7 (m, 1H), 2.5 (m, 5H), 2.8 (m, 3H), 3.1 (t, 2H), 3.5 (m, 1H), 4.1 (q, 2H), 4.3 (t, 2H), 6.6 (d, 1H), 6.8 (d, 1H), 7.5 (m, 3H), 8.1 (m, 2H); MS (ES) 422 $(M+1)^+$; HPLC RT 3.11 min.

[237] **Example 37**

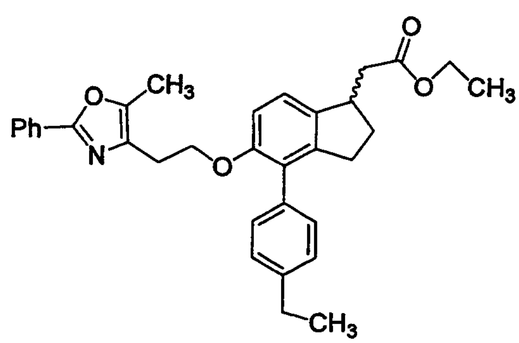
Preparation of ethyl (5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-4-{[(trifluoromethyl)sulfonyl]oxy}-2,3-dihydro-1*H*-inden-1-yl)acetate



[238] To a solution of ethyl {4-hydroxy-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate (0.46 g,1.1 mmol) in pyridine (3 mL) at -40°C was added triflic anhydride (0.3 mL, 1.4 mmol), then warmed to 0°C and stirred for 20 minutes. The mixture was then warmed to 23°C and stirred for 45 minutes. After the reaction was complete as shown by TLC, the mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried with sodium sulfate and the solvents were evaporated. The residue was purified by Biotage to obtain the desired product (0.39 g, 0.7 mmol) in 65% yield. ^{1}H NMR ($CDCl_3$) δ 1.3 (t, 3H), 1.7 (m, 1H), 2.5 (m, 5H), 2.7 (m, 1H), 2.9 (m, 2H), 3.1 (t, 2H), 3.6 (m, 1H), 4.1 (q, 2H), 4.3 (t, 2H), 6.8 (d, 1H), 7.1 (d, 1H), 7.5 (m, 3H), 8.0 (m, 2H); MS (ES) 553.9 $(M+1)^+$.

[239] **Example 38**

Preparation of ethyl {4-(4-ethylphenyl)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate

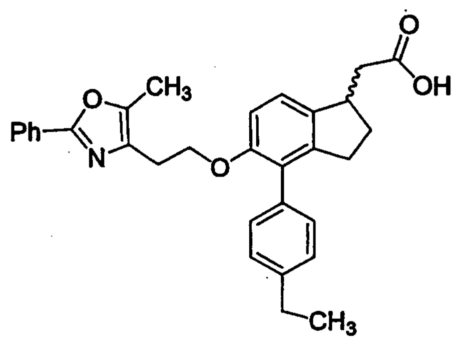


[240] To a solution containing ethyl (5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-4-{[(trifluoromethyl)sulfonyl]oxy}-2,3-dihydro-1*H*-inden-1-yl)acetate (0.5 g, 0.09 mmol), 1,1'-bis(diphenylphosphino)-ferrocene]dichloro palladium(II) (8 mg, 0.01 mmol), and 4-

ethylphenylboronic acid (0.027 g, 0.18 mmol) in degassed toluene and dioxane (4:1, 2 mL) was added aqueous 2 M sodium carbonate (0.5 mL). The mixture was heated at 85°C for 16 h. Solvents were evaporated under vacuum, and the residue was dissolved in methanol and acetonitrile and filtered through a C8 reverse phase extraction cartridge. The solvents were evaporated and the residue was dissolved in acetonitrile and purified by HPLC to obtain the desired product (0.02 g, 0.04) in 43% yield. ^1H NMR ($CDCl_3$) δ 1.3 (m, 6H), 1.7 (m, 1H), 1.8 (s, 3H), 2.3 (m, 1H), 2.5 (m, 1H), 2.7 (m, 5H), 3.0 (t, 2H), 3.6 (m, 1H), 4.2 (m, 4H), 6.8 (d, 1H), 7.1 (m, 5H), 7.6 (m, 3H), 8.0 (m, 2H); MS (ES) 510 $(M+1)^+$.

[241] **Example 39**

Preparation of {4-(4-ethylphenyl)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic acid

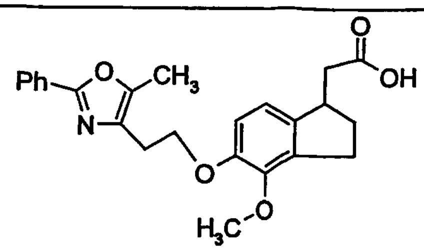
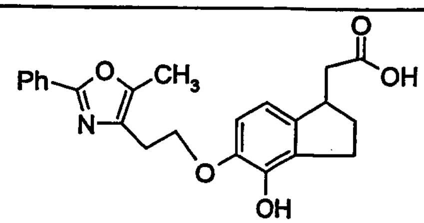
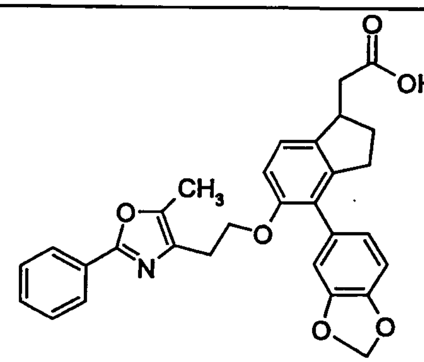
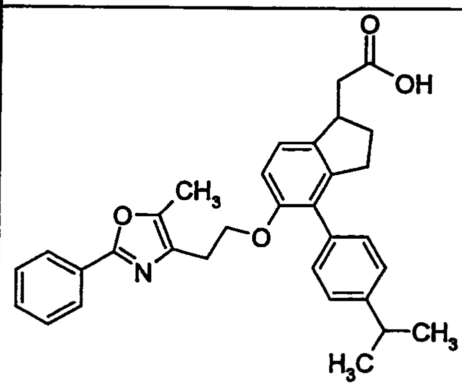


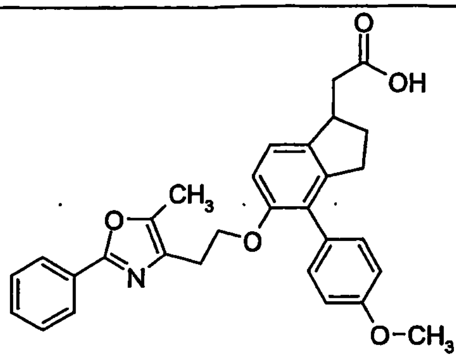
[242] {4-(4-Ethylphenyl)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate (0.02 g, 0.04 mmol) was dissolved in EtOH (1 mL), and $LiOH.H_2O$ (0.01 g, 0.21 mmol) was added. Water (1 mL) was added, and THF was added until the cloudy solution became clear. The resulting mixture was stirred overnight at rt. HCl (2N) was added to adjust the pH to 2, then extracted three times with ethyl acetate. The solvents were evaporated and the residue was purified by HPLC to obtain the desired product (0.003 g, 0.006 mmol) in 15% yield. ^1H NMR ($CDCl_3$) δ 1.3 (t, 3H), 1.7 (m, 1H), 1.8 (s, 3H), 2.3 (m, 1H), 2.5 (m, 1H), 2.7 (m, 4H), 2.9 (m, 3H), 3.6 (m, 1H), 4.2 (t, 2H), 6.8 (d, 1H), 7.1 (m, 5H), 7.5 (m, 3H), 8.0 (m, 2H); MS (ES) 482 $(M+1)^+$; HPLC RT 4.01 min.

[243] Using the methods described above for Examples 38 and 39 and the appropriate starting materials, the following compounds were similarly prepared:

[244]

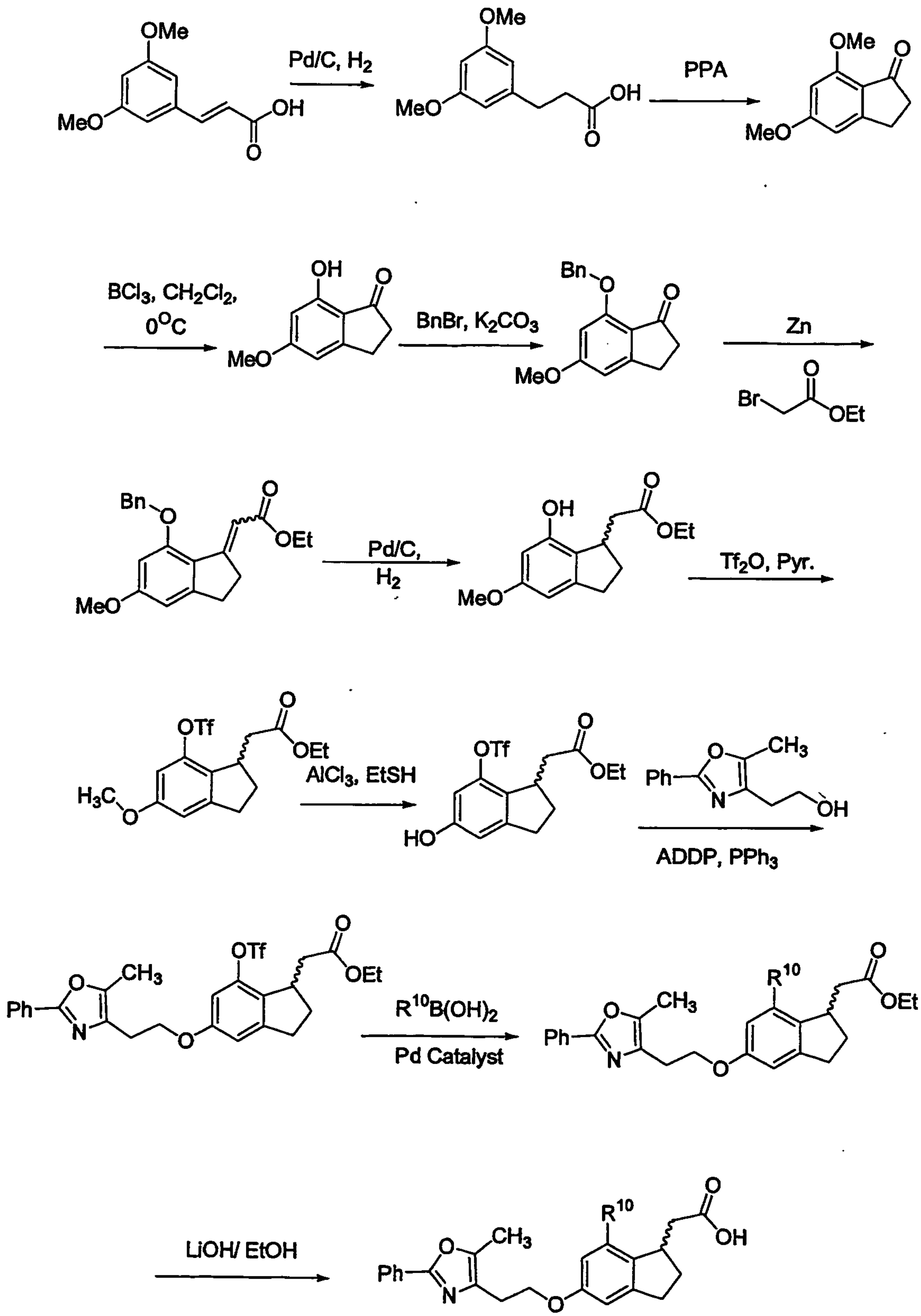
Table 3

Example No.	Structure	M+1 (ES)	RT (min)	Name
40		408	3.19	{4-methoxy-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}acetic acid
41		394	3.11	{4-hydroxy-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}acetic acid
42		498	3.58	{4-(1,3-benzodioxol-5-yl)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}acetic acid
43		496	4.15	{4-(4-isopropylphenyl)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}acetic acid

Example No.	Structure	M+1 (ES)	RT (min)	Name
44		484	3.64	{4-(4-methoxyphenyl)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}acetic acid

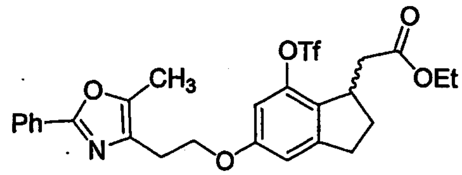
[245] Using the appropriate starting materials, Examples 45-68 were prepared by the methods exemplified in Reaction Scheme 11.

[246] **Reaction Scheme 11**

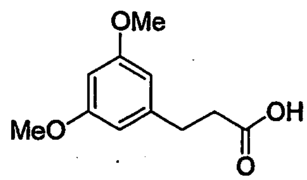


[247] Example 45

Preparation of ethyl (5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-7-{[(trifluoromethyl)sulfonyl]oxy}-2,3-dihydro-1*H*-inden-1-yl)acetate

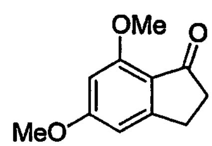


[248] Step 1. Preparation of 3-(3,5-dimethoxyphenyl)propanoic acid



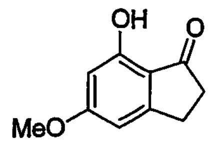
[249] To a flame dried flask under argon was added Pd/C (10%, 1 g) and ethanol (15 mL) to wet the palladium. A solution of 3-(3,5-dimethoxyphenyl)-2-propenoic acid (10 g, 48 mmol) in ethanol was added slowly to the flask containing Pd/C under argon. A hydrogen balloon was connected to the flask and stirred under hydrogen for 16 h. The reaction was filtered through a Celite® plug and the filtrate was evaporated under vacuum. The residue was purified by Biotage to obtain 3-(3,5-dimethoxyphenyl)propanoic acid (9.89 g,47 mmol) as a solid in 98% yield. ^{1}H NMR ($CDCl_3$) δ 2.7 (t, 2H), 2.9 (t, 2H), 3.8 (s, 6H), 6.4 (m, 3H); MS (ES) 211.0 $(M+H)^+$.

[250] Step 2. Preparation of 5,7-dimethoxy-1-indanone



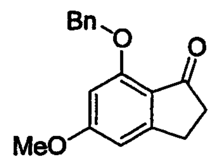
[251] To a flame dried flask under argon was added 3-(3,5-dimethoxyphenyl)propanoic acid (13 g, 62 mmol) and polyphosphoric acid (110 g,) and the mixture was stirred and heated at 70°C for 3 h. The reaction was cooled to rt, diluted with water (1 L), and poured slowly into 2 M sodium hydroxide solution (400 mL). The aqueous layer was extracted with toluene and dried with sodium sulfate. Solvents were evaporated off under vacuum to obtain 5,7-dimethoxy-1-indanone (10.35 g, 54 mmol) in 87 % yield. ^{1}H NMR ($CDCl_3$) δ 2.6 (t, 2H), 3.0 (t, 2H), 3.8 (s, 3H), 3.9 (s, 3H), 6.3 (m, 1H), 6.5 (m, 1H); GC/MS (ES) 193 $(M+1)^+$.

[252] Step 3. Preparation of 7-hydroxy-5-methoxy-1-indanone



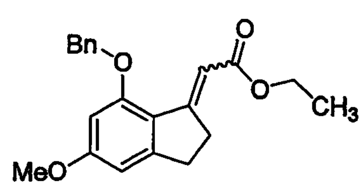
[253] To a solution of 5,7-dimethoxy-1-indanone (10.3 g, 54 mmol) in dichloromethane (100 mL) at 0°C was added 1 M solution of BCl_3 (102 mL, 102 mmol) in dichloromethane, and the resulting solution was stirred for 2.5 h at 0°C. The mixture was warmed to rt and stirred for 2.5 h. The reaction mixture was poured into 100 g ice, and the aqueous layer was extracted with dichloromethane. Solvents were evaporated under vacuum to obtain 7-hydroxy-5-methoxy-1-indanone (9.3 g, 52 mmol) in 96% yield. ^{1}H NMR ($CDCl_3$) δ 2.7 (t, 2H), 3.1 (t, 2H), 3.9 (s, 3H), 6.3 (m, 1H), 6.5 (m, 1H), 9.2 (bs, 1H); MS (ES) 179 $(M+1)^+$.

[254] Step 4. Preparation of 7-(benzyloxy)-5-methoxy-1-indanone



[255] To a solution of 7-hydroxy-5-methoxy-1-indanone (3 g, 17 mmol) in DMF (15 mL) was added to K_2CO_3 (2.8 g, 20 mmol) and the mixture was stirred for 1 h. To the reaction mixture was added benzyl bromide (2.2 mL, 19 mmol), and the reaction was stirred at 70°C for 16 h. Solvents were evaporated under vacuum and the residue was extracted with ethyl acetate and water. The organic layer was dried with sodium sulfate and solvents were evaporated under vacuum. The residue was purified by Biotage to obtain 7-(benzyloxy)-5-methoxy-1-indanone (3.3 g, 12 mmol) in 73% yield. ^{1}H NMR ($CDCl_3$) δ 2.7 (t, 2H), 3.0 (t, 2H), 3.8 (s, 3H), 5.2 (s, 2H), 6.3 (m, 1H), 6.5 (m, 1H), 7.3 (m, 3H), 7.5 (m, 2H); MS (ES) 268 $(M+)^+$.

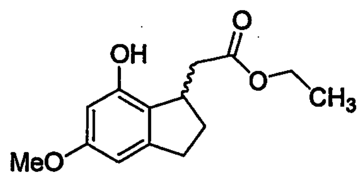
[256] Step 5. Ethyl-[7-(benzyloxy)-5-methoxy-2,3-dihydro-1*H*-inden-1-ylidene]ethanoate



[257] To a solution of 7-(benzyloxy)-5-methoxy-1-indanone (6 g, 22 mmol) in toluene/THF (50:1, 40 mL) was added with Zn powder (2.5 g, 39 mmol) and CuCl (0.4 g, 4 mmol). The reaction was stirred for 30 minutes at 90°C. The external heating was removed, and ethyl bromoacetate (3.7 mL, 34 mmol) was added, and the reaction was

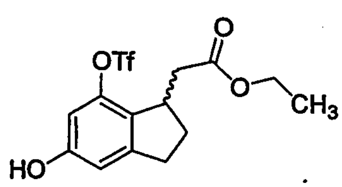
stirred at 100°C for 4 h. The reaction was cooled to rt and diluted with ether and extracted with 2N HCl. The organic layer was dried with sodium sulfate and solvents were evaporated under vacuum. The residue was purified by Biotage to obtain the desired compound (5.8 g, 17 mmol) in 77% yield. ^{1}H NMR ($CDCl_3$) δ 1.3 (t, 3H), 3.0 (t, 2H), 3.3 (t, 2H), 3.8 (s, 3H), 4.2 (q, 2H), 5.2 (s, 2H), 6.3 (m, 1H), 6.5 (m, 1H), 6.8 (s, 1H), 7.5 (m, 5H); MS (ES) 339 $(M+1)^+$.

[258] Step 6. Preparation of ethyl (7-hydroxy-5-methoxy-2,3-dihydro-1*H*-inden-1-yl)acetate



[259] To a flame dried flask under argon was added with Pd/C (10%, 0.62 g) and ethanol (15 mL) to wet the palladium. A solution of ethyl-[7-(benzyloxy)-5-methoxy-2,3-dihydro-1*H*-inden-1-ylidene]ethanoate (6.2 g, 18 mmol) in ethanol was added slowly to the flask containing Pd/C under argon. A hydrogen balloon was connected to the flask and the mixture was stirred under hydrogen for 16 h. The reaction was filtered through a Celite® plug and the filtrate was evaporated under vacuum. The residue was purified by Biotage to obtain the title compound (4.3 g, 17 mmol) as a solid in 93% yield. ^{1}H NMR ($CDCl_3$) δ 1.3 (t, 3H), 1.9 (m, 1H), 2.3 (m, 1H), 2.7 (m, 3H), 3.0 (m, 1H), 3.5 (m, 1H), 3.7 (s, 3H), 4.2 (q, 2H), 6.3 (s, 1H), 6.4 (s, 1H), 8.2 (bs, 1H); GC/MS (EI) 251 $(M+1)^+$.

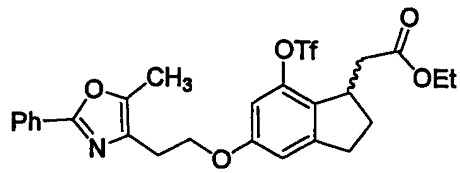
[260] Step 7. Preparation of ethyl (5-hydroxy-7-{[(trifluoromethyl)sulfonyl]oxy}-2,3-dihydro-1H-inden-1-yl)acetate



[261] To a solution of ethyl (7-hydroxy-5-methoxy-2,3-dihydro-1*H*-inden-1-yl)acetate (2 g, 8 mmol) in pyridine (20 mL) at -40°C was added triflic anhydride (1.8 mL, 10 mmol) and the mixture was warmed to 0°C and stirred for 20 minutes. The mixture was warmed to 23°C and stirred for 45 minutes. After the reaction was complete by TLC, it was quenched with water and extracted with ethyl acetate. The organic layer was dried with sodium sulfate and the solvent were evaporated. The residue (3 g) was dissolved in dichloromethane (15 mL) and cooled to 0°C, and aluminum chloride (5.3 g, 40 mmol) was added. The reaction was stirred for 5 minutes and ethane thiol (3 mL, 40 mmol) was

added. The reaction was stirred for 1 h and poured into 100 g ice water. The aqueous layer was extracted with dichloromethane. The organic layer was washed with brine and dried with sodium sulfate. Solvents were evaporated under vacuum. The residue was purified by Biotage to obtain the desired product (2.3 g, 6 mmol, 78%) as a light yellow colored oil. ^{1}H NMR ($CDCl_3$) δ 1.3 (t, 3H), 1.9 (m, 1H), 2.4 (m, 2H), 2.9 (m, 3H), 3.8(m, 1H), 4.1 (m, 2H), 5.2 (bs, 1H), 6.6 (s, 1H), 6.7(s, 1H); GC/MS (EI) 369 $(M+1)^+$.

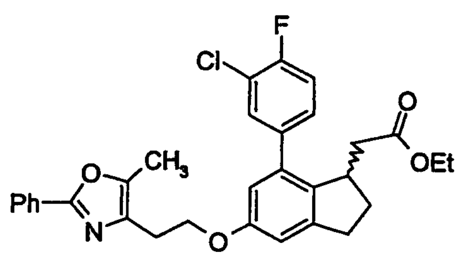
[262] <u>Step 8. Preparation of ethyl (5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-7-{[(trifluoromethyl)sulfonyl]oxy}-2,3-dihydro-1*H*-inden-1-yl)acetate</u>



[263] To a flask containing ethyl (5-hydroxy-7-{[(trifluoromethyl)sulfonyl]oxy}-2,3-dihydro-1*H*-inden-1-yl)acetate (2.1 g, 5.8 mmol), 2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethanol (1.2 g, 5.8 mmol), ADDP (2.9 g, 11.6 mmol), and triphenylphosphine (3 g, 11.6 mmol) was added THF under argon. The reaction was stirred at rt for 48 h. The solids were filtered through a silica gel plug and the filtrate was evaporated under vacuum. The residue was purified by Biotage to obtain the title compound (2.8 g, 5 mmol, 87%) as a yellow liquid. ^{1}H NMR ($CDCl_3$) δ 1.2 (t, 3H), 1.9 (m, 1H), 2.4 (m, 5H), 2.9 (m, 5H), 3.8(m, 1H), 4.2 (m, 4H), 6.6 (s, 1H), 6.8(s, 1H), 7.5 (m, 3H), 8.0 (m, 2H); /MS (ES) 554 $(M+1)^+$.

[264] **<u>Example 46</u>**

<u>Preparation of ethyl {7-(3-chloro-4-fluorophenyl)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate</u>

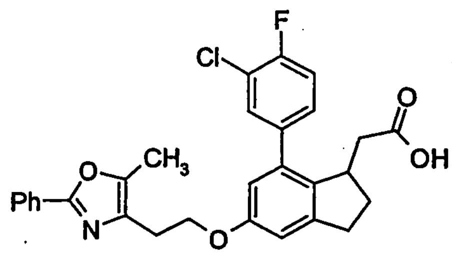


[265] To a solution containing ethyl (5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-7-{[(trifluoromethyl)sulfonyl]oxy}-2,3-dihydro-1*H*-inden-1-yl)acetate (0.100 g, 0.2 mmol), 1,1'-bis(diphenylphosphino)-ferrocene]dichloro palladium(II) (15 mg, 0.02 mmol), and 3-chloro-4-fluorophenylboronic acid (0.063 g, 0.36 mmol) in degassed toluene and dioxane (4:1, 2 mL) was added aqueous 2 M sodium carbonate (0.5 mL). The mixture was heated at 85°C for 16 h. Solvents were evaporated under vacuum, and the residue was

dissolved in methanol and acetonitrile and filtered through a C8 reverse phase extraction cartridge. Solvents were evaporated and the residue was dissolved in acetonitrile and purified by HPLC to obtain the desired product in 41% yield (40 mg, 0.07 mmol). ^1H NMR ($CDCl_3$) δ 1.2 (t, 3H), 1.9 (m, 1H), 2.0 (m, 2H), 2.4 (m, 4H), 3.0(m, 4H), 3.8 (m, 1H), 4.0 (q, 2H), 4.3(t, 2H), 6.6 (s, 1H), 6.8 (s, 1H), 7.2 (t, 1H), 7.3 (m, 1H), 7.5 (m, 4H), 8.0 (m, 2H); MS (ES) 534 $(M+)^+$.

[266] **Example 47**

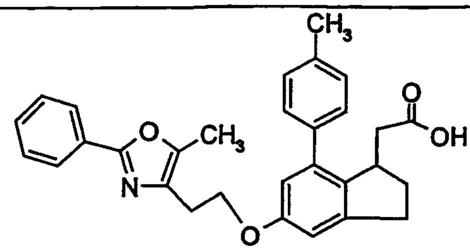
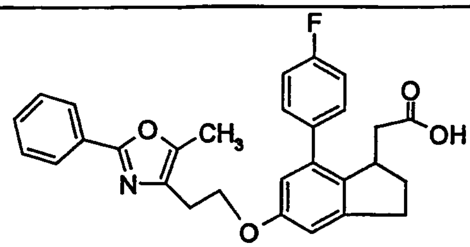
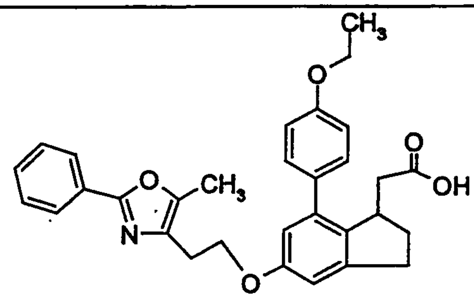
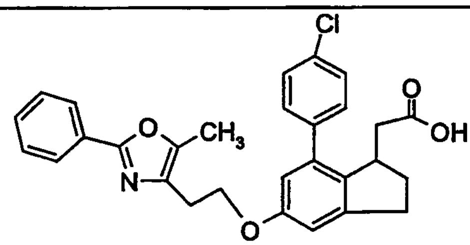
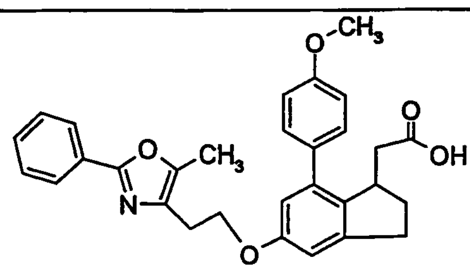
Prepatation of {7-(3-chloro-4-fluorophenyl)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic acid

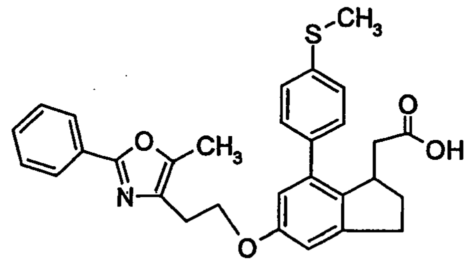
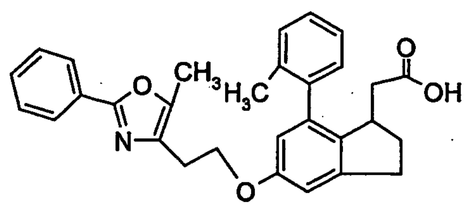
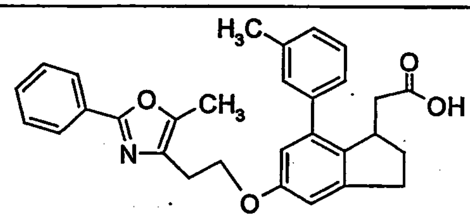
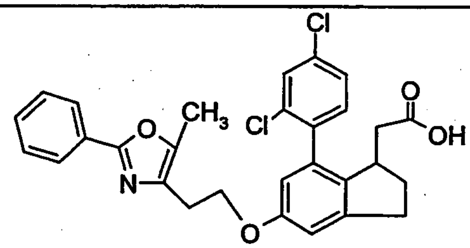
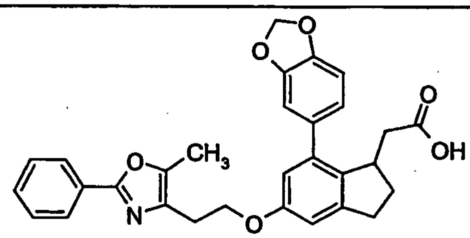
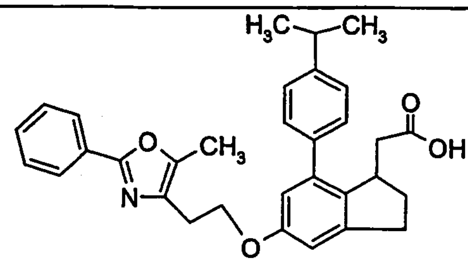


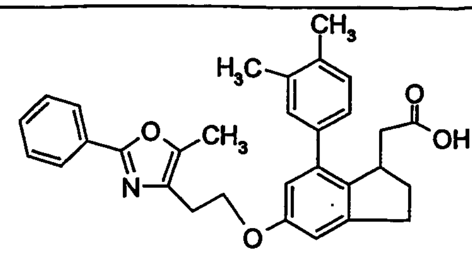
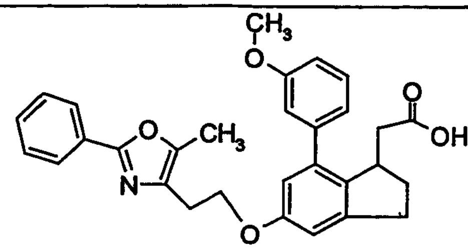
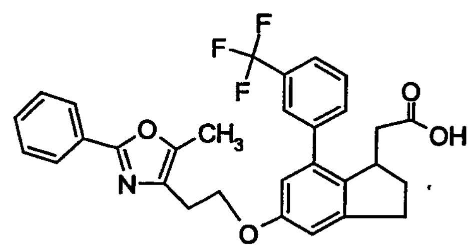
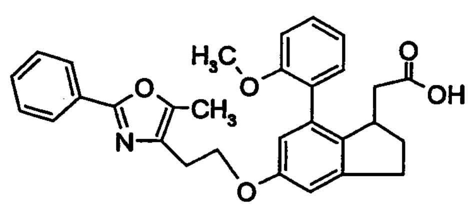
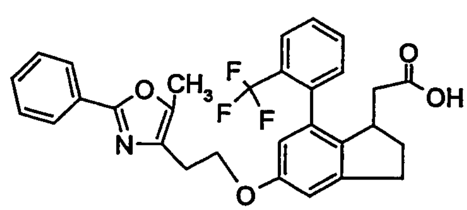
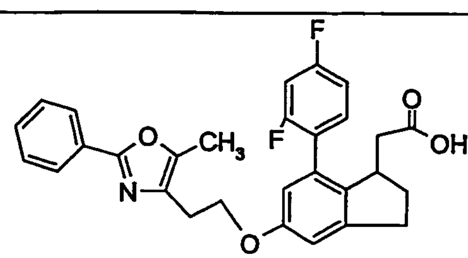
[267] Ethyl {7-(3-chloro-4-fluorophenyl)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate (0.50 g, 0.09 mmol) was dissolved in EtOH (1 mL) and $LiOH.H_2O$ (0.020 g, 0.47 mmol) was added. Water (1 mL) was added, and THF was added until the cloudy solution became clear. The resulting mixture was stirred overnight at rt. HCl (2N) was added to adjust the pH to 2, and the mixture was extracted three times with ethyl acetate. The solvents were evaporated and the residue was purified by HPLC to obtain the desired product (15 mg, 0.03 mmol, 32%). ^1H NMR ($CDCl_3$) δ 1.9 (m, 1H), 2.0 (m, 2H), 2.4 (m, 4H), 3.0(m, 4H), 3.8 (m, 1H), 4.3(t, 2H), 6.6 (s, 1H), 6.8 (s, 1H), 7.2 (t, 1H), 7.3 (m, 1H), 7.5 (m, 4H), 8.0 (m, 2H); MS (ES) 506 $(M+1)^+$; HPLC RT 4.51 min.

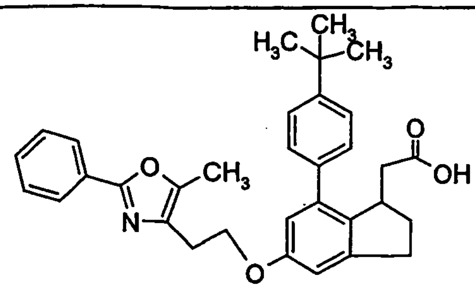
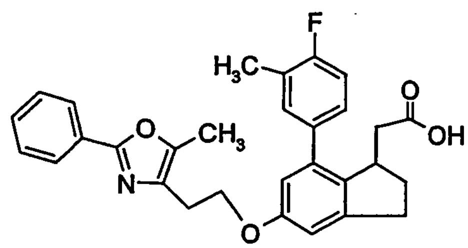
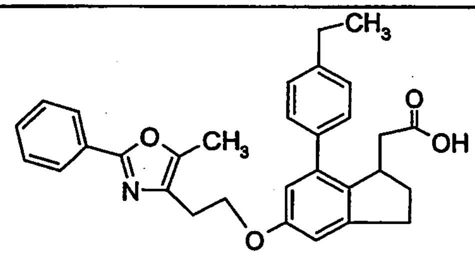
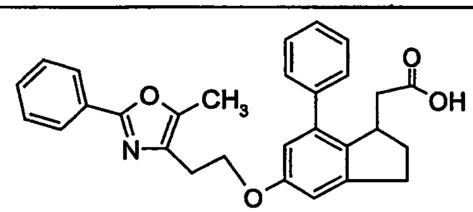
[268] Using the methods described above for Examples 45-47 and substituting the appropriate starting materials, the following compounds in Table 4 were similarly prepared:

[269] **Table 4**

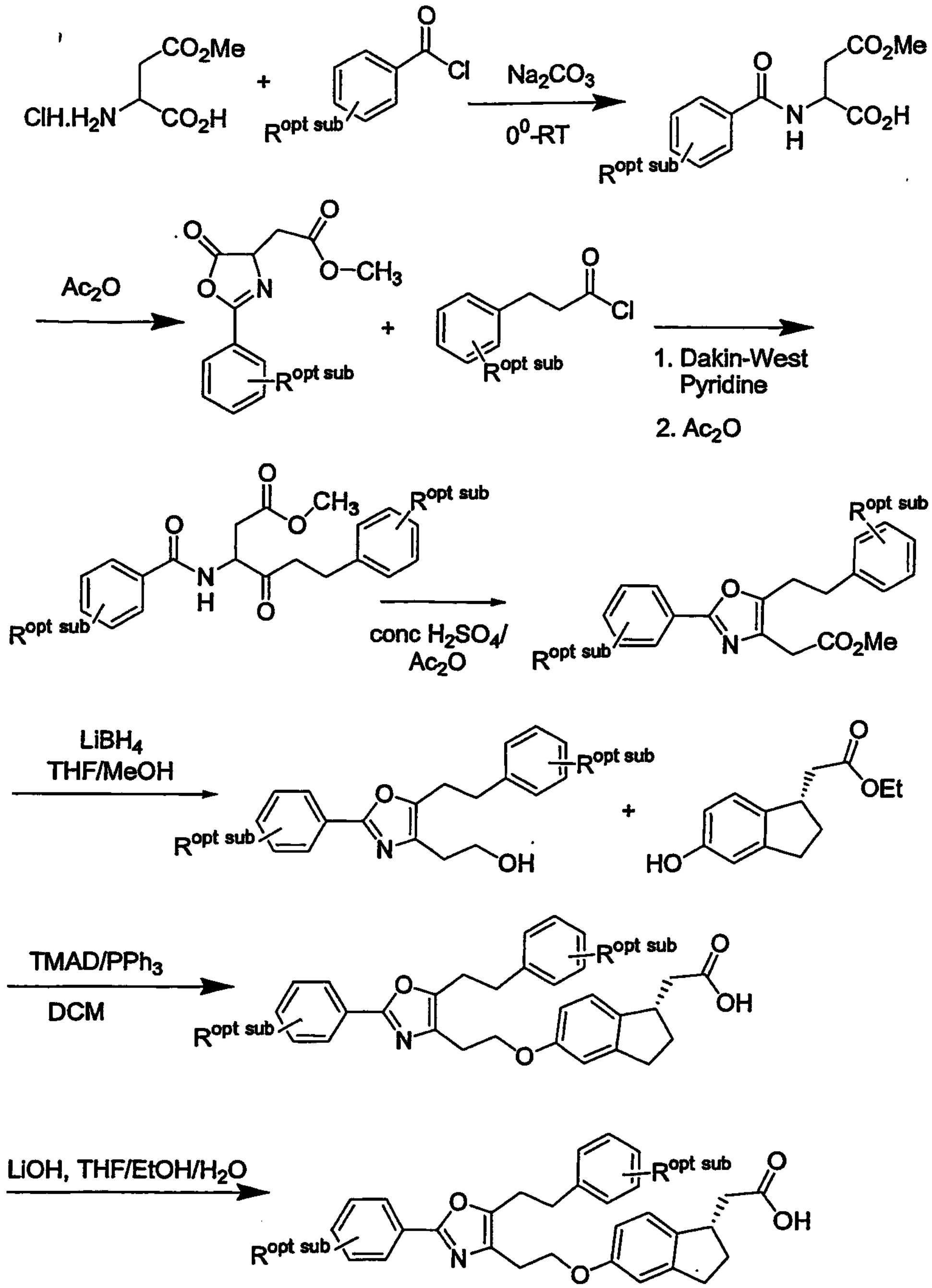
Example No.	Structure	M+1 (ES)	RT (min)	Name
48		468	4.44	{7-(4-methylphenyl)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}acetic acid
49		472	4.34	{7-(4-fluorophenyl)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}acetic acid
50		498	4.44	{7-(4-ethoxyphenyl)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}acetic acid
51		488	4.49	{7-(4-chlorophenyl)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}acetic acid
52		484	4.29	{7-(4-methoxyphenyl)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}acetic acid

Example No.	Structure	M+1 (ES)	RT (min)	Name
53		500	4.46	{5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-7-[4-(methylsulfanyl)phenyl]-2,3-dihydro-1H-inden-1-yl}acetic acid
54		468	4.41	{7-(2-methylphenyl)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}acetic acid
55		468	4.44	{7-(3-methylphenyl)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}acetic acid
56		522	4.58	{7-(2,4-dichlorophenyl)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}acetic acid
57		498	4.26	{7-(1,3-benzodioxol-5-yl)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}acetic acid
58		496	4.68	{7-(4-isopropylphenyl)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}acetic acid

Example No.	Structure	M+1 (ES)	RT (min)	Name
59		482	4.55	{7-(3,4-dimethylphenyl)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}acetic acid
60		484	4.3	{7-(3-methoxyphenyl)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}acetic acid
61		522	4.39	{5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-7-[3-(trifluoromethyl)phenyl]-2,3-dihydro-1H-inden-1-yl}acetic acid
62		484	4.25	{7-(2-methoxyphenyl)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}acetic acid
63		522	4.4	{5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-7-[2-(trifluoromethyl)phenyl]-2,3-dihydro-1H-inden-1-yl}acetic acid
64		490	4.33	{7-(2,4-difluorophenyl)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}acetic acid

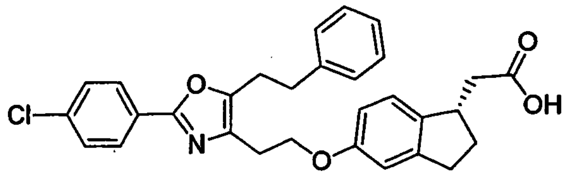
Example No.	Structure	M+1 (ES)	RT (min)	Name
65		510	4.77	{7-(4-tert-butylphenyl)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}acetic acid
66		486	4.47	{7-(4-fluoro-3-methylphenyl)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}acetic acid
67		482	4.57	{7-(4-ethylphenyl)-5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}acetic acid
68		454	4.31	{5-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-7-phenyl-2,3-dihydro-1H-inden-1-yl}acetic acid

[270] **Reaction Scheme 12**

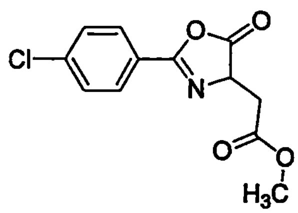


[271] **Example 69**

Preparation of (1S)-(5-{2-[2-(4-chloro-phenyl)-5-phenethyl-oxazol-4-yl]-ethoxy}-indan-1-yl)-acetic acid

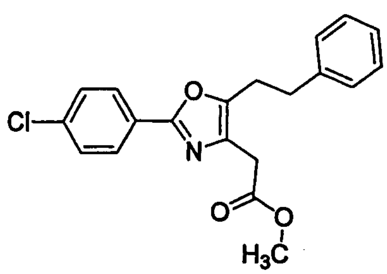


[272] Step1: Preparation of [2-(4-Chloro-phenyl)-5-oxo-4,5-dihydro-oxazol-4-yl]-acetic acid methyl ester



[273] To L-aspartic acid β-methyl ester hydrochloride (5.0 g, 27.2 mmol) in a water (100 mL) and acetone (10 mL) solution was added Na_2CO_3 (10.10 g, 95.3 mmol) at 0^oC. The mixture was stirred at 0^oC for 1 h. 4-Chloro-benzoyl chloride (3.8 mL, 32.7 mmol) was added dropwise, and the mixture was allowed to warm to ambient temperature slowly with stirring for 1h. The pH of the reaction mixture was adjusted to 3 by adding 1N HCl. The reaction mixture was then extracted with EtOAc (3 x 100 mL) and dried over Na_2SO_4, concentrated and dried under vacuum. The obtained white solid was then dissolved in acetic anhydride (42 mL) and toluene (12 mL) solution. The reaction was heated at 50°C for 2 h. The solvent was then removed under reduced pressure. The solid was washed with hot hexane (3 x 50 mL) and dried under vacuum. The product (5.5 g, 20.5 mmol, 76%) was obtained as a white solid.

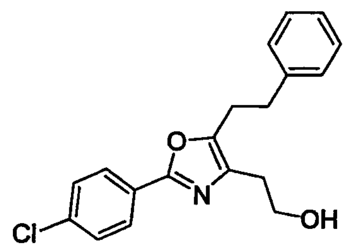
[274] Step 2: Preparation of [2-(4-Chloro-phenyl)-5-phenethyl-oxazol-4-yl]-acetic acid methyl ester



[275] The intermediate prepared in Step 1 (233 mg, 1.00 mmol) was dissolved in pyridine (0.5 mL) at 0^oC. 3-Phenyl-propionyl chloride (132 μL, 1.2 mmol) was then added to the solution. The reaction mixture was stirred at rt for 1h, and then at 55^oC for 2h.

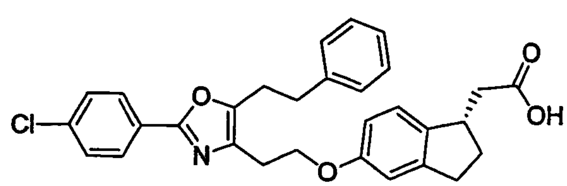
Acetic acid (300 µL) was then added to the solution, and the mixture was stirred for another 2 h at 55°C. The reaction mixture was cooled down to ambient temperature, poured into water (5 mL), and extracted with EtOAc (3 x 10 mL). The organic layer was washed with 1N HCl, sat. $NaHCO_3$, and then brine solution. The organic layer was dried over Na_2SO_4 and concentrated to afford a dark yellow oil. The oil was then dissolved in acetic anhydride (1.0 mL) followed by slow addition of conc. H_2SO_4 (60 µL). The reaction was heated at 90°C for 20 minutes, cooled, and the acetic anhydride was removed *in vacuo*. The residue was poured into ice water (5 mL), and the pH was adjusted to 7 by adding 1N NaOH. The residue was extracted with EtOAc (3 x 10 mL). The organic layer was dried with Na_2SO_4 and concentrated to afford the title ester as a clear oil. The oil was subjected to the next step without purification.

[276] Step 3: Preparation of 2-[2-(4-Chloro-phenyl)-5-phenethyl-oxazol-4-yl]-ethanol



[277] The oxazole ester prepared in Step 2 was dissolved in THF (2.0 mL) and 2 M $LiBH_4$ solution (1.0 mL) was added to the solution. Anhydrous MeOH (100 µL) was then added to initiate the reaction. The reaction was stirred at 40°C for 15 h. The reaction mixture was cooled to ambient temperature and poured into water (5 mL). The mixture was neutralized to pH 7 by adding 1N HCl solution. The residue was extracted with EtOAc (3 x 10 mL). The organic layer was dried with Na_2SO_4 and concentrated. The residue was purified by prep-TLC (50% EtOAc/hexane) to give a white solid as product (49.0 mg, 0.15 mmol, 15%). LC-MS(M+H): 294, RT: 2.66 min.

[278] Step 4: Preparation of (1S)-(5-{2-[2-(4-chlorophenyl)-5-phenyl-5-phenethyl-oxazole-4-yl]-ethoxy}-indan-1-yl)-acetic acid

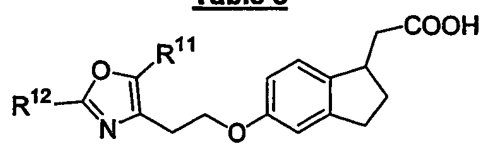


[279] Using the same Mitsunobu reaction procedure as described in Example 12, Step 5, 2[2-(4-Chloro-phenyl)-5-phenethyl-oxazol-4-yl]-ethanol was reacted with ethyl [(1S)-5-hydroxy-2,3-dihydro-1*H*-inden-1-yl)]acetate to give (1S)-(5-{2-[2-(4-chloro-phenyl)-5-phenethyl-oxazol-4-yl]-ethoxy}-indan-1-yl)-acetic acid ethyl ester as an intermediate.

Followed by the hydrolysis reaction as described in Example 2 to give (1S)-(5-{2-[2-(4-chloro-phenyl)-5-phenethyl-oxazol-4-yl]-ethoxy}-indan-1-yl)-acetic acid as final product. ^1H NMR ($CDCl_3$-d_1): δ 1.73(m, 1H), 2.35-3.48 (m, 2H), 2.73-3.03 (m, 9H), 3.51 (m, 1H), 4.03 (t, 2H), 6.60 (dd, 1H), 6.72 (s, 1H), 7.06 (d, 1H), 7.13-7.30 (m, 5H), 7.41(m, 2H), 7.90 (m, 2H). LC-MS(MH^+):503.4, 3.75min.

[280] By using the methods described for Example 69 above, compounds listed in Tables 5-6 were similarly prepared.

[281] **Table 5**



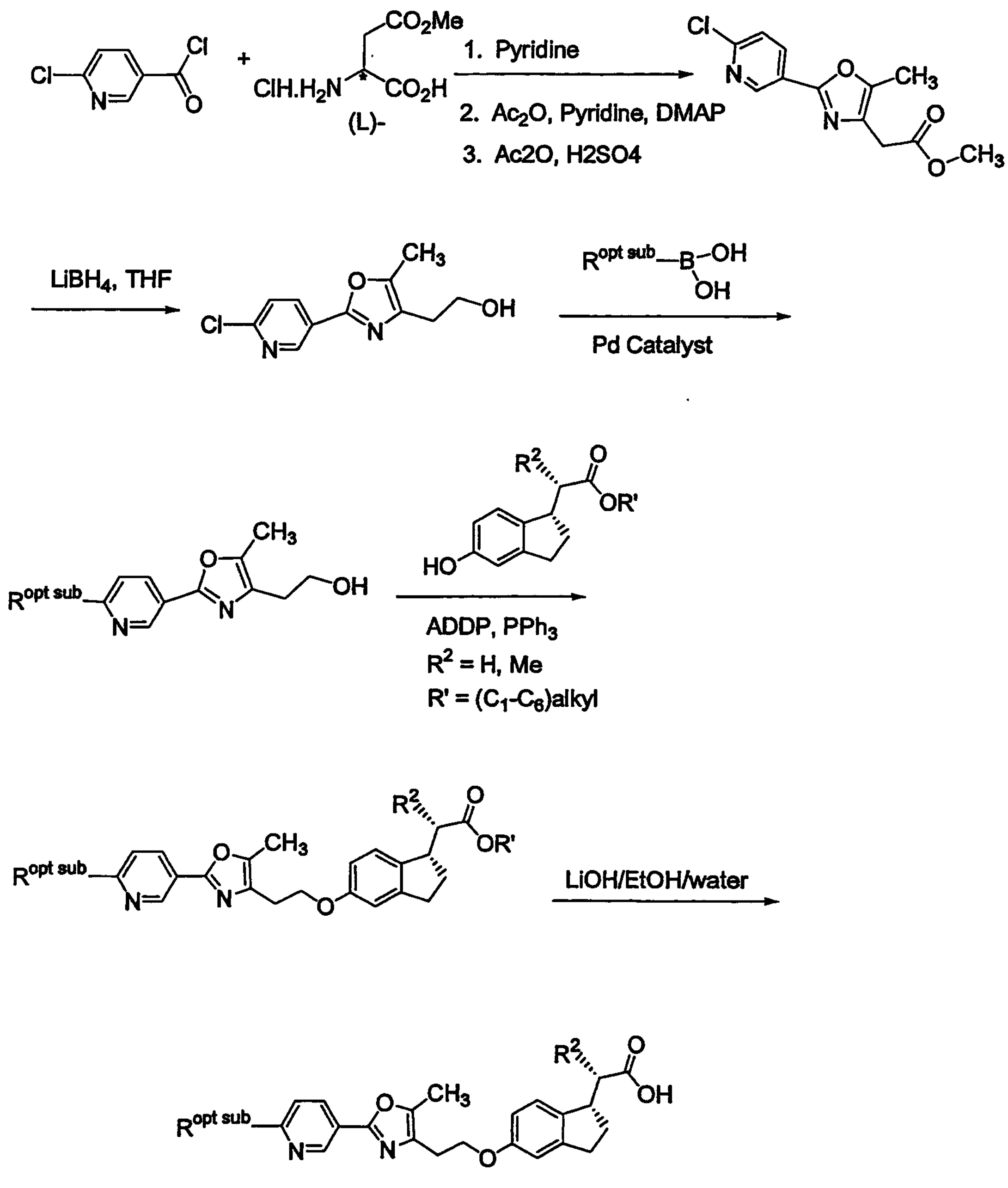
Example No.	R^{11}	R^{12}	LC/MS [M + H]+
70	Ph-CH_2CH_2-	Ph	468.5
71	4-MeO-Ph-CH_2CH_2-	4-Cl-Ph	533.5
72	2,6-$(Cl)_2$-Ph-CH_2CH_2-	4-Cl-Ph	571.4
73	3-Me-Ph-CH_2CH_2-	4-Cl-Ph	517.5
74	4-Me-Ph-CH_2CH_2-	4-Cl-Ph	517.5
75	4-Cl-Ph-CH_2CH_2-	4-Cl-Ph	537.4

[282] **Table 6**

Example No.	IUPAC Name
70	(1*S*)-{5-[2-(5-Phenethyl-2-phenyl-oxazol-4-yl)-ethoxy]-indan-1-yl}-acetic acid
71	(1*S*)-[5-(2-{2-(4-Chloro-phenyl)-5-[2-(4-methoxy-phenyl)-ethyl]-oxazol-4-yl}-ethoxy)-indan-1-yl]-acetic acid
72	(1*S*)-[5-(2-{2-(4-Chloro-phenyl)-5-[2-(2,6-dichloro-phenyl)-ethyl]-oxazol-4-yl}-ethoxy)-indan-1-yl]-acetic acid
73	(1*S*)-[5-{2-[2-(4-Chloro-phenyl)-5-(2-m-tolyl-ethyl)-oxazol-4-yl]-ethoxy}-indan-1-yl)-acetic acid
74	(1*S*)-[5-{2-[2-(4-Chloro-phenyl)-5-(2-p-tolyl-ethyl)-oxazol-4-yl}-ethoxy}-indan-1-yl)-acetic acid
75	(1*S*)-[5-(2-{2-(4-Chloro-phenyl)-5-[2-(4-chloro-phenyl)-ethyl]-oxazol-4-yl}-ethoxy)-indan-1-yl]-acetic acid

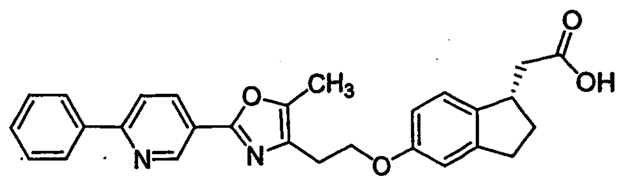
[283] Using the appropriate starting materials, Examples 76-77 were prepared by the method exemplified in Reaction Scheme 13.

[284] **Reaction Scheme 13**

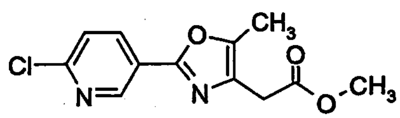


[285] **Example 76**

Preparation of ((1*S*)-5-{2-[5-methyl-2-(6-phenyl-3-pyridinyl)-1,3-oxazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid

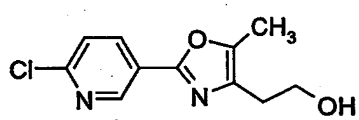


[286] Step 1. Preparation of methyl [2-(6-chloro-3-pyridinyl)-5-methyl-1,3-oxazol-4-yl]acetate



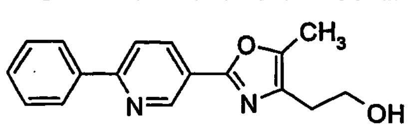
[287] Methyl [2-(6-chloro-3-pyridinyl)-5-methyl-1,3-oxazol-4-yl]acetate was prepared starting from 6-chloro-nicotinoyl chloride and L-aspartic acid methyl ester hydrochloride following the procedure for Intermediate F in oxazole synthesis (Steps 1-2). ^{1}H NMR (CD_2Cl_2) δ 2.4 (s, 3H), 3.5 (s, 2H), 3.7 (s, 3H), 7.4 (d, 1H), 8.3 (m, 1H), 9.0 (m, 1H); MS (ES) 267 $(M+1)^+$.

[288] Step 2. Preparation of 2-[2-(6-chloro-3-pyridinyl)-5-methyl-1,3-oxazol-4-yl]ethanol



[289] To a solution of methyl [2-(6-chloro-3-pyridinyl)-5-methyl-1,3-oxazol-4-yl]acetate (1.3 g, 5 mmol) in THF(10 mL) was added methanol (0.5 mL), 2M solution of $LiBH_4$ (3.2 mL, 6.3 mmol) in THF, and water (0.1 mL). The reaction was stirred for 1.5 h and quenched with water (100 mL). The pH of the solution was adjusted to 5 with slow addition of 2 M aqueous HCl. The aqueous layer was extracted with ethyl acetate and dried with sodium sulfate. The solvents were evaporated off under vacuum and the residue was purified by biotage to obtain 2-[2-(6-chloro-3-pyridinyl)-5-methyl-1,3-oxazol-4-yl]ethanol (0.45 g, 2 mmol) as a white solid in 37% yield. ^{1}H NMR (CD_2Cl_2) δ 2.4 (s, 3H), 2.7 (t, 2H), 3.9 (t, 2H), 7.4 (d, 1H), 8.3 (m, 1H), 9.0 (m, 1H); MS (ES) 239 $(M+1)^+$.

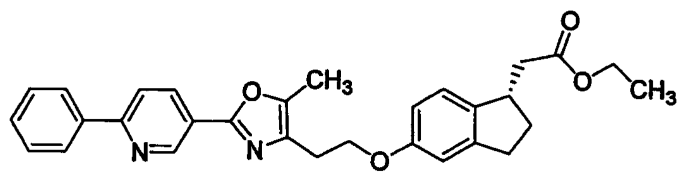
[290] Step 3. Preparation of 2-[5-methyl-2-(6-phenyl-3-pyridinyl)-1,3-oxazol-4-yl]ethanol



[291] To a solution containing 2-[2-(6-chloro-3-pyridinyl)-5-methyl-1,3-oxazol-4-yl]ethanol (0.100 g, 0.4 mmol), 1,1'-bis(diphenylphosphino)-ferrocene]dichloro palladium(II) (34 mg,

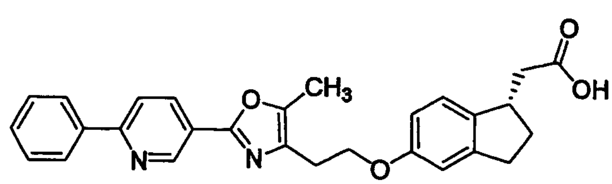
0.04 mmol), and phenylboronic acid (0.066 g, 0.5 mmol) in degassed toluene and dioxane (4:1, 3 mL) was added aqueous 2 M sodium carbonate (1 mL). The mixture was heated at 85°C for 16 h. Solvents were evaporated under vacuum, and the residue was dissolved in methanol and acetonitrile and filtered through a C8 reverse phase extraction cartridge. Solvents were evaporated and the residue was dissolved in acetonitrile and purified by biotage to obtain 2-[5-methyl-2-(6-phenyl-3-pyridinyl)-1,3-oxazol-4-yl]ethanol (0.11 g, 0.4 mmol) in 93% yield. ^{1}H NMR (CD_2Cl_2) δ 2.4 (s, 3H), 2.7 (t, 2H), 3.9 (t, 2H), 7.5 (m, 3H),7.9 (d, 1H), 8.1 (m, 2H), 8.3 (m, 1H), 9.0 (m, 1H); MS (ES) 281 $(M+1)^+$.

[292] Step 4. Preparation of ethyl ((1*S*)-5-{2-[5-methyl-2-(6-phenyl-3-pyridinyl)-1,3-oxazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetate



[293] To a flask containing 2-[5-methyl-2-(6-phenyl-3-pyridinyl)-1,3-oxazol-4-yl]ethanol (0.05 g, 0.2 mmol), ethyl [(1*S*)-5-hydroxy-2,3-dihydro-1*H*-inden-1-yl]acetate (0.043 g, 0.2 mmol), TMAD (0.06 g, 0.4 mmol), and triphenylphosphine (0.09 g, 0.4 mmol) was added with THF (0.5 mL) under argon. The reaction was stirred at rt for 16 h. The solids were filtered through a silica gel plug and the filtrate was evaporated under vacuum. The residue was purified by biotage to obtain the desired product (0.05 g, 0.1 mmol) in 56% yield. ^{1}H NMR ((CD_2Cl_2) δ 1.3 (m, 3H), 1.7 (m, 1H), 2.4 (m, 5H), 2.8 (m, 3H), 3.0 (t, 2H), 3.5 (m, 1H), 4.2 (q, 2H), 4.3 (t, 2H), 6.7 (m, 1H), 6.8 (s, 1H), 7.1 (d, 1H), 7.5 (m, 3H), 7.9 (d, 1H), 8.1 (d, 2H), 8.3 (m, 1H), 9.3 (s, 1H); MS (ES) 483 $(M+1)^+$.

[294] Step 5. Preparation of ((1*S*)-5-{2-[5-methyl-2-(6-phenyl-3-pyridinyl)-1,3-oxazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid

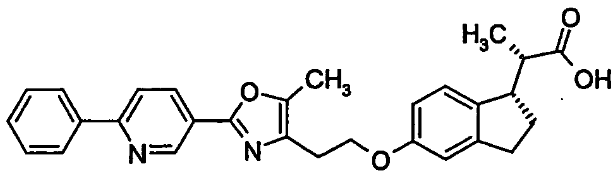


[295] Ethyl ((1*S*)-5-{2-[5-methyl-2-(6-phenyl-3-pyridinyl)-1,3-oxazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetate (0.50 g, 0.1 mmol) was dissolved in EtOH (1 mL), and $LiOH.H_2O$ (0.022 g, 0.5 mmol) was added. Water (1 mL) was added, and THF was added until the cloudy solution became clear. The resulting mixture was stirred overnight at rt. HCl (2N) was added to adjust the pH to 2, and the mixture was extracted three times with ethyl acetate. The solvents were evaporated and the residue was purified by

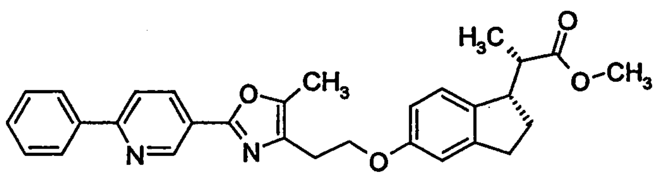
HPLC to obtain the title compound (0.012 g, 0.03 mmol) in 24% yield. ^{1}H NMR (CD_2Cl_2) δ 1.8 (m, 1H), 2.4 (m, 5H), 2.8 (m, 3H), 3.0 (t, 2H), 3.5 (m, 1H), 4.3 (t, 2H), 6.7 (m, 1H), 6.8 (s, 1H), 7.1 (d, 1H), 7.5 (m, 3H), 7.9 (d, 1H), 8.1 (d, 2H), 8.3 (m, 1H), 9.3 (s, 1H); MS (ES) 455 $(M+1)^+$; HPLC RT 3.88 min.

[296] **Example 77**

Preparation of (2S)-2-((1S)-5-{2-[5-methyl-2-(6-phenyl-3-pyridinyl)-1,3-oxazol-4-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)propanoic acid

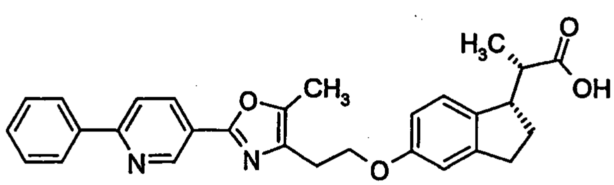


[297] Step 1: Methyl (2S)-2-((1S)-5-{2-[5-methyl-2-(6-phenyl-3-pyridinyl)-1,3-oxazol-4-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)propanoate



[298] Using a similar procedure to Step 4, Example 76 above, and by substituting (2S)-2-((1S)-5-hydroxy-indan-1-yl)-propionic acid methyl ester (Intermediate A) as starting material, the title compound was prepared. ^{1}H NMR (CD_2Cl_2) δ 1.1 (d, 3H), 1.9 (m, 1H), 2.2 (m, 1H), 2.4 (s, 3H), 2.8 (m, 3H), 3.0 (t, 2H), 3.5 (m, 1H), 3.7 (s, 3H), 4.3 (t, 2H), 6.7 (m, 1H), 6.8 (s, 1H), 7.0 (d, 1H), 7.5 (m, 3H), 7.9 (d, 1H), 8.1 (d, 2H), 8.3 (m, 1H), 9.3 (s, 1H); MS (ES) 483 $(M+1)^+$.

[299] Step 2: (2S)-2-((1S)-5-{2-[5-methyl-2-(6-phenyl-3-pyridinyl)-1,3-oxazol-4-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)propanoic acid

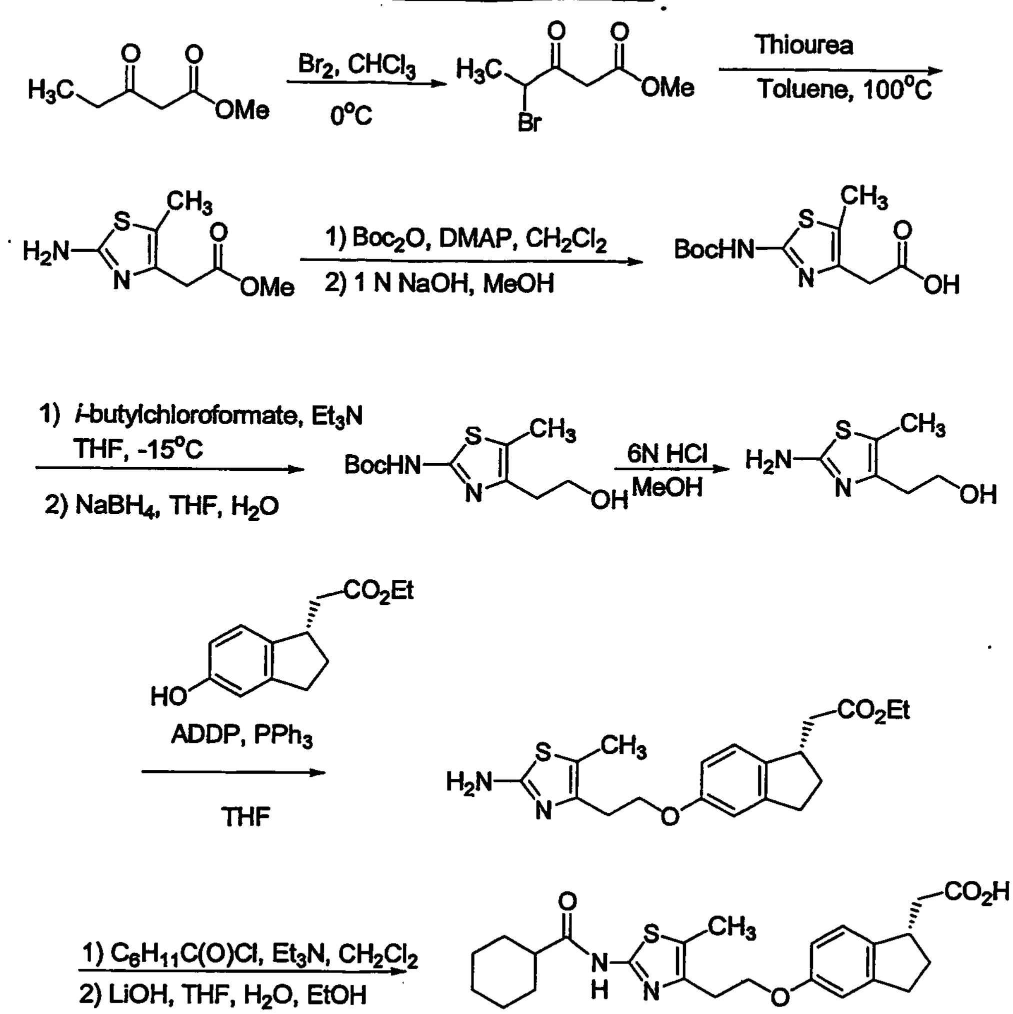


[300] Using a similar procedure to Step 5, Example 76 above, and by using the product from Step 1 above as starting material, the title compound was prepared. ^{1}H NMR (CD_2Cl_2) δ 1.1 (d, 3H), 1.9 (m, 1H), 2.2 (m, 1H), 2.4 (s, 3H), 2.8 (m,3H), 3.0 (t, 2H), 3.6 (m, 1H), 4.3 (t, 2H), 6.7 (m, 1H), 6.8 (s, 1H), 7.1 (d, 1H), 7.5 (m, 3H), 7.9 (d, 1H), 8.1 (d, 2H), 8.3 (m, 1H), 9.3 (s, 1H); MS (ES) 469 $(M+1)^+$; HPLC RT 4.00 min.

[301] **Preparation of Thiazoles**

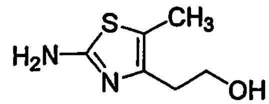
Reaction Scheme 14 summarizes the synthetic methods utilized for the preparation of compounds of Formula (Ia) where X = S. These methods were used to prepare Intermediate H, Intermediate I, and Examples 78-107, as specifically described below.

[302] **Reaction Scheme 14**

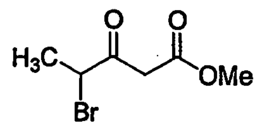


[303] **Intermediate H**

Preparation of 2-(2-amino-5-methyl-1,3-thiazol-4-yl)ethanol

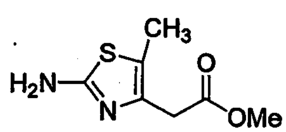


[304] Step 1: Preparation of methyl 4-bromo-3-oxopentanoate



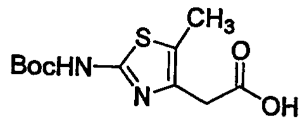
A dry three-neck flask under an argon atmosphere was charged with a solution of methyl propionylacetate (20 g, 154 mmol) in $CHCl_3$ (100 mL). Using an addition funnel, bromine (7.9 mL, 24.6 g, 154 mmol) was added dropwise over a period of 2 h at 0°C. The reaction was then allowed to warm slowly to rt, and the reaction mixture was stirred overnight. A saturated solution of Na_2CO_3 (40 mL) was slowly added, and after stirring the reaction mixture for an additional 15 minutes, the solvent layers were separated. The aqueous layer was extracted with CH_2Cl_2 (50 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was then purified by silica gel flash chromatography (10:1 hexanes/EtOAc) to give the bromide as a light yellow oil (25 g, 78%). ^1H NMR ($CDCl_3$): δ 1.80 (d, 3H), 3.64-3.92 (m, 2H), 3.78 (s, 3H), 4.61 (q, 1H).

[305] Step 2: Preparation of methyl (2-amino-5-methyl-1,3-thiazol-4-yl)acetate



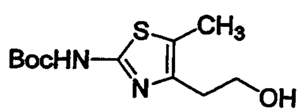
[306] To a solution of bromide from Step 1 (18 g, 86 mmol) in toluene (100 mL) was added thiourea (10.5 g, 138 mmol). The reaction mixture was heated to 100°C for 1 h, cooled to rt, and the solvent removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 mL), a saturated solution of $NaHCO_3$ (75 mL) was added, and the mixture was vigorously stirred for 10 minutes. The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was then recrystallized from CH_2Cl_2/hexanes to provide the product (10 g, 63%) as a white solid. ($C_7H_{10}N_2O_2S$): LC-MS, RT 0.76 min, $(M+H)^+$ 187.0; ^1H NMR ($CDCl_3$): δ 2.23 (s, 3H), 3.70 (s, 2H), 3.75 (s, 3H), 4.83-4.95 (broad s, 2H).

[307] Step 3: Preparation of {2-[(*tert*-butoxycarbonyl)amino]-5-methyl-1,3-thiazol-4-yl}acetic acid



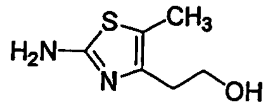
[308] To a solution of the compound prepared in Step 2 (5.00 g, 26.8 mmol) and DMAP (32 mg, 0.26 mmol) in CH_2Cl_2 (150 mL) was added BOC_2O (7.00 g, 32.2 mmol). After 4 h, additional quantities of BOC_2O (7.00 g, 32.2 mmol) and Et_3N (7.50 mL, 53.6 mmol) were added. The reaction mixture was stirred at rt for 18 h, then a saturated solution of NH_4Cl (100 mL) was added and the reaction was stirred for 15 minutes. The layers were separated, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was passed through a short plug of silica gel to yield a mixture of the corresponding mono- and di-carbamate. This mixture was dissolved in MeOH (40 mL), and a 1N solution of NaOH (20 mL) was added. The solution was stirred for 90 minutes, the methanol removed under reduced pressure and the residue was washed with Et_2O (2 x 10 mL). The aqueous layer was acidified to pH ~ 4 using 1N HCl, extracted with CH_2Cl_2 (2 x 50 mL), and the combined organic layers dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford the desired product as a yellow solid (4.4 g, 60%). ($C_{11}H_{16}N_2O_4S$): LC-MS, RT 2.39 min, $(M+H)^+$ 272.9; ^1H NMR ($CDCl_3$): δ 1.51 (s, 9H), 2.32 (s, 3H), 3.61 (s, 2H).

[309] Step 4: Preparation of *tert*-butyl 4-(2-hydroxyethyl)-5-methyl-1,3-thiazol-2-ylcarbamate



[310] To a solution of the compound prepared in Step 3, (4.4 g, 16 mmol) and Et_3N (2.5 mL, 18 mmol) in THF (80 mL) was added isobutyl chloroformate (2.3 mL, 18 mmol) at –15°C. The reaction mixture was stirred at –15°C for 2 h, the solids were removed by filtration, and a solution of $NaBH_4$ (3.0 g, 80 mmol) in H_2O (10 mL) was then added to the filtrate [strong gaseous evolution]. After 5 minutes, an additional amount of water (100 mL) was added, and the aqueous phase was extracted with EtOAc (3 x 200 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified using silica gel flash chromatography (1:1 hexanes/EtOAc) to furnish the product (2.3 g, 55%) as a colorless oil. ($C_{11}H_{18}N_2O_3S$): LC-MS, RT 2.14 min, $(M+H)^+$ 259.0; ^1H NMR ($CDCl_3$): δ 1.53 (s, 9H), 2.27 (s, 3H), 2.78 (t, 2H), 3.89 (t, 2H).

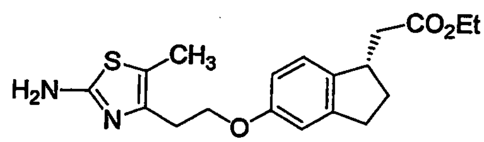
[311] Step 5: Preparation of 2-(2-amino-5-methyl-1,3-thiazol-4-yl)ethanol



[312] To a solution of the compound prepared in Step 4 (2.0 g, 7.8 mmol) in MeOH (25 mL) was added a 6N aqueous solution of HCl (25 mL). The mixture was vigorously stirred at rt for 20 h, the methanol removed under reduced pressure, and the remaining solution neutralized (pH ~ 8) using a saturated solution of $NaHCO_3$. The product was then extracted with CH_2Cl_2 (4 x 200 mL), the combined organic layers dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give the product (795 mg, 65%) as a beige foam. ($C_6H_{10}N_2OS$): LC-MS RT, 0.75 min, $(M+H)^+$ 159.0; ^1H NMR ($CDCl_3$): δ 2.15 (s, 3H), 2.64 (t, 2H), 3.80 (t, 2H), 4.69-5.04 (broad, 2H).

[313] **Intermediate I**

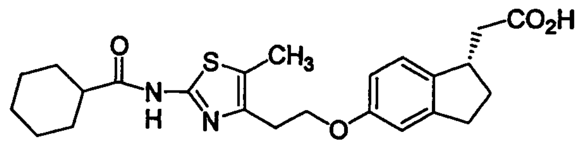
Preparation of ethyl {(1*S*)-5-[2-(2-amino-5-methyl-1,3-thiazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate



[314] To a solution of Intermediate H (710 mg, 6.33 mmol) and (Intermediate D, 1.26 g, 5.76 mmol) in THF (25 mL) were added Ph_3P (2.56 g, 9.79 mmol) and ADDP (2.47 g, 9.79 mmol). The mixture was vigorously stirred at rt for 72 h, and then the solvent was removed under reduced pressure. The residue was purified by silica gel flash chromatography (7:3 hexanes/EtOAc) to yield the coupled product as the Ph_3P=O/amino group adduct (1.2 g, 33%). This phosphine oxide adduct was then treated with 1N HCl (10 mL) in THF (10 mL) for 18 h. The THF was removed under reduced pressure, and the remaining aqueous solution was washed with Et_2O (3 x 50 mL). The aqueous layer was basified using a saturated solution of $NaHCO_3$ and the product extracted with CH_2Cl_2 (3 x 100 mL). The ether and CH_2Cl_2 layers were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (6:4 hexanes/EtOAc to 4:1 EtOAc/MeOH) to yield the product (384 mg, 56%) as a yellowish oil. ($C_{19}H_{24}N_2O_3S$): LC-MS RT, 2.43 min, $(M+H)^+$ 361.2; ^1H NMR ($CDCl_3$): δ 1.20 (t, 3H), 1.58-1.76 (m, 1H), 2.51 (s, 3H), 2.23-2.35 (m, 2H), 2.56-2.90 (m, 5H), 3.36-3.50 (m, 1H), 3.99-4.17 (m, 4H), 4.62-5.11 (broad, 2H), 6.61 (d, 1H), 6.68 (s, 1H), 6.96 (d, 1H).

[315] **Example 78**

Preparation of [(1*S*)-5-(2-{2-[(cyclohexylcarbonyl)amino]-5-methyl-1,3-thiazol-4-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic acid

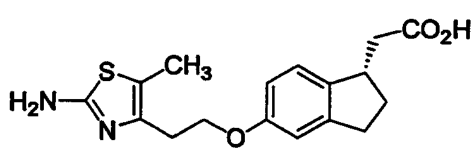


[316] Step 1. To a solution of amine Intermediate I (19 mg, 0.053 mmol) in CH_2Cl_2 was added Et_3N (0.015 mL, 0.11 mmol) and cyclohexanecarbonyl chloride (0.015 mL, 0.11 mmol), and the solution was stirred at rt. Upon completion of the reaction by TLC analysis, the reaction mixture was diluted with a saturated solution of $NaHCO_3$ and the product extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure.

[317] Step 2. The residue was then dissolved in a mixture of THF (1 mL), EtOH (0.5 mL) and water (1 mL), LiOH (15 mg, 0.625 mmol) was added, and the mixture was stirred at rt for 4 h. The solution was then washed with Et_2O (5 mL), the aqueous phase acidified to pH ~2 using 1N HCl, and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide the title compound (12.6 mg, 53%) as a white solid. ($C_{24}H_{30}N_2O_4S$): LC-MS, RT 3.16 min, $(M+H)^+$ 443.4; ^1H NMR ($CDCl_3$): δ 1.20-2.00 (m, 12H), 2.36 (s, 3H), 2.40-2.85 (m, 5H), 3.05 (t, 2H), 3.54-3.55 (m, 1H), 4.13 (t, 2H), 6.66 (d, 1H), 6.69 (s, 1H), 7.07 (d, 1H).

[318] **Example 79**

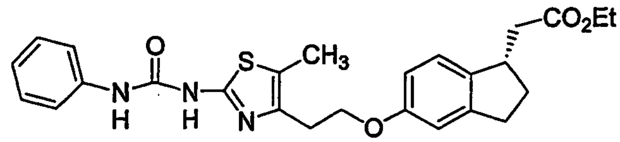
Preparation of {(1*S*)-5-[2-(2-amino-5-methyl-1,3-thiazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic acid



[319] This compound was prepared by the hydrolysis of Intermediate I, using a procedure similar to that of Step 2, Example 78. Concentration of the solution and purification by HPLC to give the TFA salt of the amine. ($C_{17}H_{20}N_2O_3S.C_2HF_3O_2$): LC-MS, RT 2.07 min, $(M+H)^+$ 333.2; ^1H NMR (CD_3CN): δ 1.61-1.79 (m, 1H), 2.20 (s, 3H), 2.23-2.48 (m, 2H), 2.61-2.88 (m, 3H), 2.93 (t, 2H), 3.34-3.48 (m, 1H), 4.17 (t, 2H), 6.70 (d, 1H), 6.79 (s, 1H), 7.10 (s, 1H), 8.58-8.75 (broad s, 2H).

[320] **Example 80**

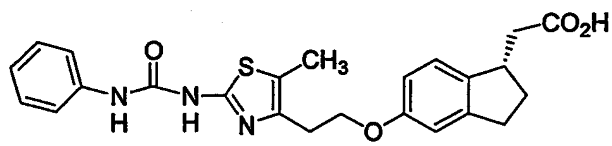
Preparation of ethyl [(1*S*)-5-(2-{2-[(anilinocarbonyl)amino]-5-methyl-1,3-thiazol-4-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetate



[321] To a solution of amine Intermediate I (21 mg, 0.057 mmol) was added phenylisocyanate (0.13 mL, 0.12 mmol) in toluene (5 mL), and the solution was stirred at rt for 30 minutes. EtOAc (50 mL) was then added, and the organic solution was washed with a saturated solution of NH_4Cl, 2N HCl, and brine sequentially. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure, and the residue purified by silica gel flash chromatography (2:1 hexanes/EtOAc) to yield the product (10 mg, 37%). ^1H NMR ($CDCl_3$): δ 1.20 (t, 3H), 1.55-1.75 (m, 1H), 2.23 (s, 3H), 2.25-2.38 (m, 2H), 2.57-2.83 (m, 3H), 2.97 (t, 2H), 3.36-3.49 (m, 1H), 4.01-4.21 (m, 4H), 6.59 (d, 1H), 6.67 (s, 1H), 6.97 (d, 1H), 6.98-7.06 (m, 1H), 7.15-7.30 (m, 2H), 7.30-7.45 (m, 2H).

[322] **Example 81**

Preparation of [(1*S*)-5-(2-{2-[(anilinocarbonyl)amino]-5-methyl-1,3-thiazol-4-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic acid

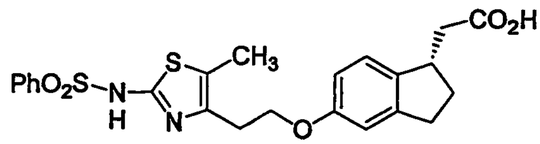


[323] Hydrolysis of the ester prepared in Example 80 was then carried out as described above for Step 2, Example 78 to give the desired product. ($C_{24}H_{25}N_3O_4S$): LC-MS, RT 2.99 min, $(M+H)^+$ 452.0; ^1H NMR ($CDCl_3$): δ 1.69-1.74 (m, 1H), 2.34 (s, 3H), 2.22-2.41 (m, 2H), 2.60-2.90 (m, 3H), 3.07(t, 2H), 3.41-3.50 (m, 1H), 4.19 (t, 2H), 6.69 (d, 1H), 6.70 (s, 1H), 7.07 (d, 1H), 7.11 (d, 1H), 7.32 (t, 2H), 7.42-7.52 (m, 2H).

[324] Using the methods described above for Example 80, Example 81, and Intermediate I, and the appropriate acyl halide, sulfonyl chloride, chloroformate, or dicarbonate as starting materials, the compounds of Examples 82-104 were prepared and characterized. In some instances, a catalytic amount of DMAP was added to increase the rate of reaction. The products were purified by silica gel chromatography or preparative HPLC when necessary.

[325] **Example 82**

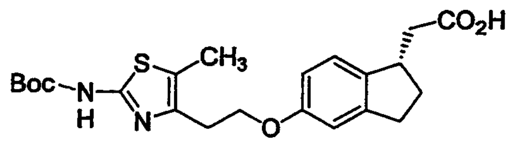
Preparation of [(1*S*)-5-(2-{5-methyl-2-[(phenylsulfonyl)amino]-1,3-thiazol-4-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic acid



[326] ($C_{23}H_{24}N_2O_5S_2$): LC-MS, RT 2.86 min, $(M+H)^+$ 473.3; ^1H NMR ($CDCl_3$): δ 1.50-1.71 (m, 1H), 2.13 (s, 3H), 2.17-2.41 (m, 2H), 2.50-2.79 (m, 3H), 2.93 (t, 2H), 3.25-3.41 (m, 1H), 4.03 (t, 2H), 6.56 (d, 1H), 6.64 (s, 1H), 6.94 (d, 1H), 7.29-7.52 (m, 3H), 7.84 (d, 2H).

[327] **Example 83**

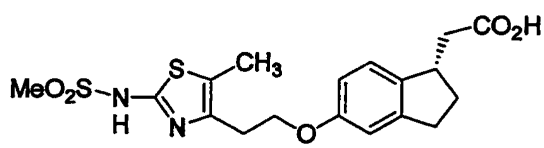
Preparation of [(1*S*)-5-(2-{2-[(*tert*-butoxycarbonyl)amino]-5-methyl-1,3-thiazol-4-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic acid



[328] ($C_{22}H_{28}N_2O_5S$): LC-MS, RT 3.27 min, $(M+H)^+$ 433.0; ^1H NMR ($CDCl_3$): δ 1.54 (s, 9H), 1.65-1.84 (m, 1H), 2.36 (s, 3H), 2.36-2.50 (m, 2H), 2.71-3.03 (m, 3H), 3.09 (t, 2H), 3.43-3.58 (m, 1H), 4.18 (t, 2H), 6.65 (d, 1H), 6.74 (s, 1H), 7.07 (s, 1H).

[329] **Example 84**

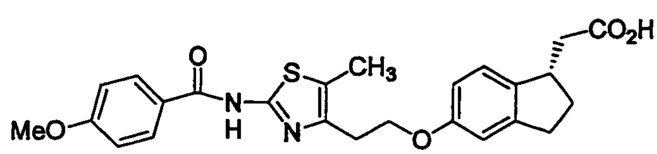
Preparation of [(1*S*)-5-(2-{5-methyl-2-[(methylsulfonyl)amino]-1,3-thiazol-4-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic acid



[330] ($C_{18}H_{22}N_2O_5S_2$): LC-MS, RT 2.52 min, $(M+H)^+$ 411.0; ^1H NMR (CD_3OD): δ 1.68-1.72 (m, 1H), 2.17 (s, 3H), 2.29-2.37 (m, 2H), 2.62-2.86 (m, 3H), 2.90 (s, 3H), 2.91 (t, 2H), 3.40-3.44 (m, 1H), 4.09 (t, 2H), 6.65 (d, 1H), 6.73 (s, 1H), 7.05 (d, 1H).

[331] **Example 85**

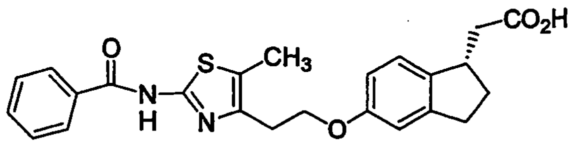
Preparation of [(1*S*)-5-(2-{2-[(4-methoxybenzoyl)amino]-5-methyl-1,3-thiazol-4-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic acid



[332] ($C_{25}H_{26}N_2O_5S$): LC-MS, RT 3.31 min, $(M+H)^+$ 467.2; ^1H NMR ($CDCl_3$): δ 1.62-1.69 (m, 1H), 2.31 (s, 3H), 2.57-2.79 (m, 4H), 3.05 (t, 2H), 3.35-3.49 (m, 2H), 3.80 (s, 3H), 4.12 (t, 2H), 6.62 (d, 1H), 6.70 (s, 1H), 6.92-7.00 (m, 3H), 8.00 (d, 2H).

[333] **Example 86**

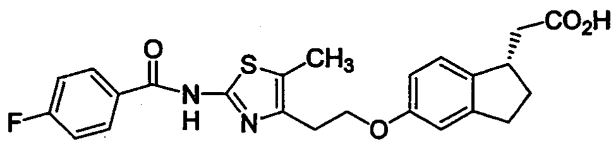
Preparation of ((1*S*)-5-{2-[2-(benzoylamino)-5-methyl-1,3-thiazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid



[334] ($C_{24}H_{24}N_2O_4S$): LC-MS, RT 3.35 min, $(M+H)^+$ 437.2; ^1H NMR ($CDCl_3$): δ 1.70-1.80 (m, 1H), 2.41 (s, 3H), 2.64-2.85 (m, 4H), 3.10 (t, 2H), 3.47-3.56 (m, 2H), 4.17 (t, 2H), 6.70 (d, 1H), 6.79 (s, 1H), 7.10 (d, 1H), 7.50-7.60 (m, 3H), 8.20 (d, 2H).

[335] **Example 87**

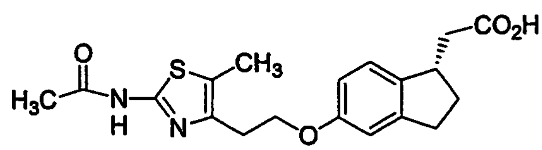
Preparation of [(1*S*)-5-(2-{2-[(4-Fluorobenzoyl)amino]-5-methyl-1,3-thiazol-4-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic acid



[336] ($C_{24}H_{23}FN_2O_4S$): LC-MS, RT 3.39 min, $(M+H)^+$ 455.2; ^1H NMR ($CDCl_3$): δ 1.62-1.72 (m, 1H), 2.36 (s, 3H), 2.20-2.40 (m, 2H), 2.57-2.80 (m, 3H), 3.07 (broad s, 2H), 3.38-3.49 (m, 1H), 4.13 (s, 2H), 6.65 (d, 1H), 6.73 (s, 1H), 7.10 (d, 1H), 7.13 (t, 2H), 8.25 (t, 2H).

[337] **Example 88**

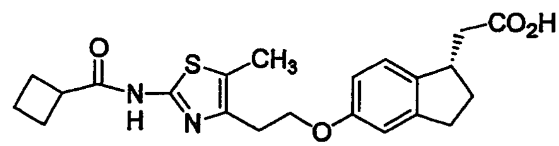
Preparation of ((1*S*)-5-{2-[2-(acetylamino)-5-methyl-1,3-thiazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid



[338] ($C_{19}H_{22}N_2O_4S$): LC-MS, RT 2.71 min, $(M+H)^+$ 375.2; ^1H NMR ($CDCl_3$): δ 1.67-1.77 (m, 1H), 2.26 (s, 3H), 2.36 (s, 3H), 2.41-2.49 (m, 1H), 2.61-2.90 (m, 4H), 3.03 (t, 2H), 3.44-3.52 (m, 1H), 4.11 (t, 2H), 6.66 (d, 1H), 6.75 (s, 1H), 7.07 (d, 1H).

[339] **Example 89**

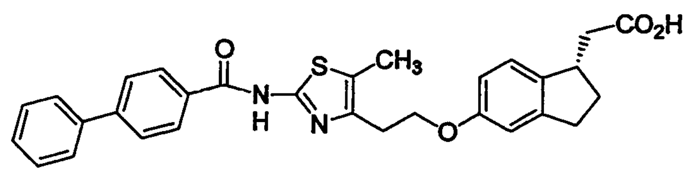
Preparation of [(1*S*)-5-(2-{2-[(cyclobutylcarbonyl)amino]-5-methyl-1,3-thiazol-4-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic acid



[340] ($C_{22}H_{26}N_2O_4S$): LC-MS, RT 2.90 min, $(M+H)^+$ 415.3; ^1H NMR ($CDCl_3$): δ 1.67-1.77 (m, 1H), 2.36 (s, 3H), 1.90-2.50 (m, 7H), 2.60-2.91 (m, 4H), 3.05 (t, 2H), 3.30-3.50 (m, 2H), 4.13 (t, 2H), 6.66 (d, 1H), 6.75 (s, 1H), 7.05 (d, 1H).

[341] **Example 90**

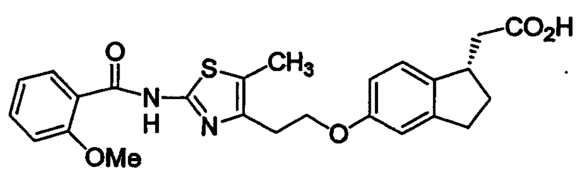
Preparation of [(1*S*)-5-(2-{2-[(1,1'-biphenyl-4-ylcarbonyl)amino]-5-methyl-1,3-thiazol-4-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic acid



[342] ($C_{30}H_{28}N_2O_4S$): LC-MS, RT 3.65 min, $(M+H)^+$ 513.3; ^1H NMR ($CDCl_3$): δ 1.70-1.80 (m, 1H), 2.43 (s, 3H), 2.34-2.52 (m, 2H), 2.65-2.90 (m, 3H), 3.12 (t, 2H), 3.45-3.55 (m, 1H), 4.19 (t, 2H), 6.74 (d, 1H), 6.81 (s, 1H), 7.10 (d, 1H), 7.40-7.49 (m, 3H), 7.63 (d, 2H), 7.75 (d, 2H), 8.30 (d, 2H).

[343] **Example 91**

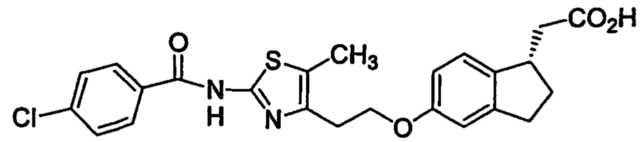
Preparation of [(1*S*)-5-(2-{2-[(2-methoxybenzoyl)amino]-5-methyl-1,3-thiazol-4-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic acid



[344] ($C_{25}H_{26}N_2O_5S$): LC-MS, RT 3.24 min, $(M+H)^+$ 467.4; ^1H NMR ($CDCl_3$): δ 1.60-1.70 (m, 1H), 2.35 (s, 3H), 2.25-2.40 (m, 2H), 2.60-2.85 (m, 3H), 3.12 (t, 2H), 3.38-3.48 (m, 1H), 4.00 (s, 3H), 4.20 (t, 2H), 6.60 (d, 1H), 6.70 (s, 1H), 6.90-7.10 (m, 3H), 7.50-7.55 (m, 1H), 8.10-8.16 (m, 1H).

[345] **Example 92**

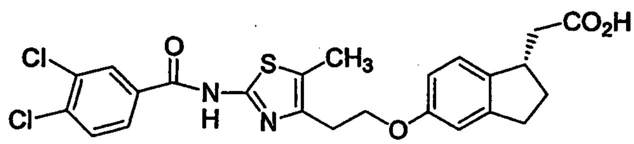
Preparation of [(1*S*)-5-(2-{2-[(4-chlorobenzoyl)amino]-5-methyl-1,3-thiazol-4-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic acid



[346] ($C_{24}H_{23}ClN_2O_4S$): LC-MS, RT 3.47 min, $(M+H)^+$ 471.1; ^1H NMR ($CDCl_3$): δ 1.45-1.55 (m, 1H), 2.20 (s, 3H), 2.30-2.60 (m, 4H), 2.91 (t, 2H), 3.17-3.27 (m, 2H), 3.98 (t, 2H), 6.49 (d, 1H), 6.58 (s, 1H), 6.92 (d, 1H), 7.12 (d, 2H), 7.67 (d, 2H).

[347] **Example 93**

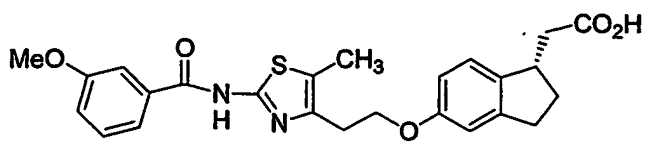
Preparation of [(1*S*)-5-(2-{2-[(3,4-dichlorobenzoyl)amino]-5-methyl-1,3-thiazol-4-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic acid



[348] ($C_{24}H_{22}Cl_2N_2O_4S$): LC-MS, RT 3.70 min, $(M+H)^+$ 505.1; ^1H NMR ($CDCl_3$): δ 1.55-1.65 (m, 1H), 2.20 (s, 3H), 2.25-2.75 (m, 4H), 2.95 (t, 2H), 3.25-3.35 (m, 2H), 4.13 (t, 2H), 6.50 (d, 1H), 6.60 (s, 1H), 6.95 (d, 1H), 7.42 (d, 1H), 7.65 (d, 1H), 7.99 (s, 1H).

[349] **Example 94**

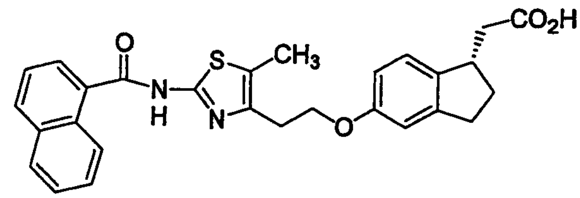
Preparation of [(1*S*)-5-(2-{2-[(3-methoxybenzoyl)amino]-5-methyl-1,3-thiazol-4-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic acid



[350] ($C_{25}H_{26}N_2O_5S$): LC-MS, RT 3.31 min, $(M+H)^+$ 467.2; ^1H NMR ($CDCl_3$): δ 1.55-1.65 (m, 1H), 2.30 (s, 3H), 2.40-2.75 (m, 4H), 3.00 (t, 2H), 3.25-3.35 (m, 2H), 3.80 (s, 3H), 4.13 (t, 2H), 6.62 (d, 1H), 6.78 (s, 1H), 7.05 (d, 1H), 7.15 (d, 1H), 7.40 (t, 1H), 7.58-7.65 (m, 2H).

[351] **Example 95**

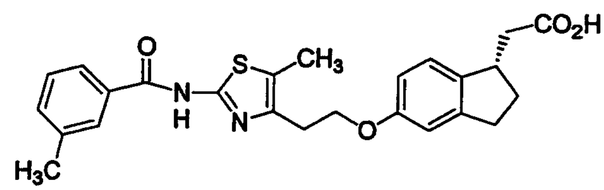
Preparation of ((1S)-5-{2-[5-methyl-2-(1-naphthoylamino)-1,3-thiazol-4-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)acetic acid



[352] ($C_{28}H_{26}N_2O_4S$): LC-MS, RT 3.46 min, $(M+H)^+$ 487.2; ^1H NMR ($CDCl_3$): δ 1.63-1.73 (m, 1H), 2.23-2.33 (m, 2H), 2.35 (s, 3H), 2.60-2.80 (m, 3H), 2.98 (t, 2H), 3.35-3.43 (m, 1H), 4.15 (t, 2H), 6.62 (d, 1H), 6.68 (s, 1H), 7.00 (d, 1H), 7.48-7.53 (m, 3H), 7.72 (d, 1H), 7.85 (d, 1H), 7.98 (d, 1H), 8.30 (d, 1H).

[353] **Example 96**

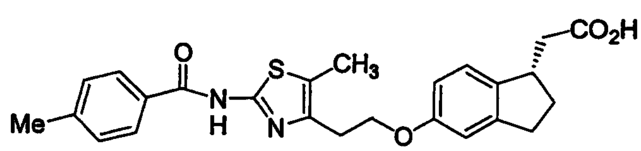
Preparation of [(1S)-5-(2-{5-methyl-2-[(3-methylbenzoyl)amino]-1,3-thiazol-4-yl}ethoxy)-2,3-dihydro-1H-inden-1-yl]acetic acid



[354] ($C_{25}H_{26}N_2O_4S$): LC-MS, RT 3.40 min, $(M+H)^+$ 451.2; ^1H NMR ($DMSO_{d6}$): δ 1.54-1.64 (m, 1H), 2.20 (m, 2H), 2.25 (s, 3H), 2.30 (s, 3H), 2.58-2.80 (m, 3H), 2.95 (t, 2H), 3.22 (m, 1H), 4.15 (t, 2H), 6.62 (d, 1H), 6.72 (s, 1H), 7.05 (d, 1H), 7.28-7.32 (m, 2H), 7.80 (d, 1H), 7.83 (s, 1H).

[355] **Example 97**

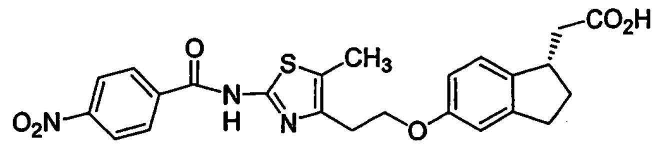
Preparation of [(1S)-5-(2-{5-methyl-2-[(4-methylbenzoyl)amino]-1,3-thiazol-4-yl}ethoxy)-2,3-dihydro-1H-inden-1-yl]acetic acid



[356] ($C_{25}H_{26}N_2O_4S$): LC-MS, RT 3.39 min, $(M+H)^+$ 451.2; ^1H NMR ($DMSO_{d6}$): δ 1.55-1.65 (m, 1H), 2.17-2.27 (m, 2H), 2.25 (s, 3H), 2.28 (s, 3H), 2.60-2.85 (m, 3H), 3.00 (t, 2H), 3.20 (m, 1H), 4.18 (t, 2H), 6.70 (d, 1H), 6.78 (s, 1H), 7.05 (d, 1H), 7.32 (d, 2H), 7.98 (d, 2H).

[357] Example 98

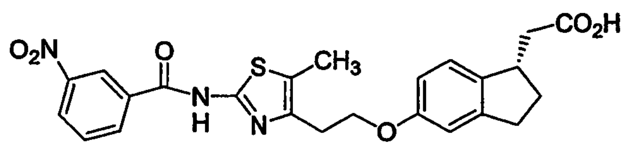
Preparation of [(1*S*)-5-(2-{5-methyl-2-[(4-nitrobenzoyl)amino]-1,3-thiazol-4-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic acid



[358] ($C_{24}H_{23}N_3O_6S$): LC-MS, RT 3.32 min, $(M+H)^+$ 482.1; ^{1}H NMR (DMSO$_{d6}$): δ 1.53-1.63 (m, 1H), 2.18-2.28 (m, 2H), 2.29 (s, 3H), 2.58-2.78 (m, 3H), 2.97 (t, 2H), 3.25-3.35 (m, 1H, overlap with water peak), 4.14 (t, 2H), 6.64 (d, 1H), 6.73 (s, 1H), 7.04 (d, 1H), 8.25 (d, 2H), 8.30 (d, 2H).

[359] Example 99

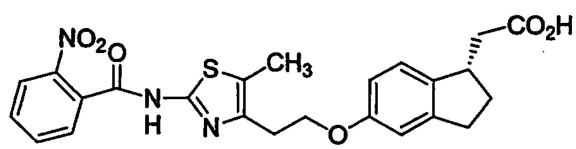
Preparation of [(1*S*)-5-(2-{5-methyl-2-[(3-nitrobenzoyl)amino]-1,3-thiazol-4-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic acid



[360] ($C_{24}H_{23}N_3O_6S$): LC-MS, RT 3.32 min, $(M+H)^+$ 482.1; ^{1}H NMR (DMSO-d6): δ 1.54-1.64 (m, 1H), 2.17-2.27 (m, 2H), 2.30 (s, 3H), 2.58-2.78 (m, 3H), 2.98 (t, 2H), 3.26-3.36 (m, 1H, overlap with water peak), 4.13 (t, 2H), 6.65 (d, 1H), 6.74 (s, 1H), 7.05 (d, 1H), 7.78 (s, 1H), 8.25-8.29 (m, 1H), 8.41 (d, 1H), 8.44 (d, 1H), 8.87 (s, 1H).

[361] Example 100

Preparation of [(1*S*)-5-(2-{5-methyl-2-[(2-nitrobenzoyl)amino]-1,3-thiazol-4-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic acid

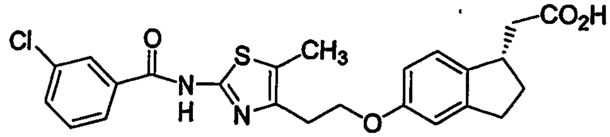


[362] ($C_{24}H_{23}N_3O_6S$): LC-MS, RT 3.09 min, $(M+H)^+$ 482.2; ^{1}H NMR (DMSO$_{d6}$): δ 1.55-1.65 (m, 1H), 2.20-2.25 (m, 2H), 2.30 (s, 3H), 2.58-2.78 (m, 3H), 2.95 (t, 2H), 3.25-3.40 (m, 1H, overlap with water peak), 4.12 (t, 2H), 6.64 (d, 1H), 6.72 (s, 1H), 7.05 (d, 1H), 7.70-7.75 (m, 2H), 7.81 (t, 1H), 8.10 (d, 1H).

[363]

Example 101

Preparation of [(1*S*)-5-(2-{2-[(3-chlorobenzoyl)amino]-5-methyl-1,3-thiazol-4-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic acid

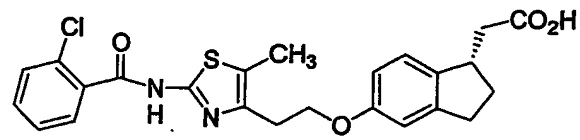


[364] ($C_{24}H_{23}ClN_2O_4S$): LC-MS, RT 3.46 min, $(M+H)^+$ 471.1; ^1H NMR ($DMSO_{d6}$): δ 1.54-1.64 (m, 1H), 2.19-2.28 (m, 2H), 2.30 (s, 3H), 2.58-2.78 (m, 3H), 2.97 (t, 2H), 3.35-3.47 (m, 1H, overlap with water peak), 4.13 (t, 2H), 6.64 (d, 1H), 6.73 (s, 1H), 7.05 (d, 1H), 7.51 (t, 1H), 7.64 (d, 1H), 7.98 (d, 1H), 8.09 (s, 1H).

[365]

Example 102

Preparation of [(1*S*)-5-(2-{2-[(2-chlorobenzoyl)amino]-5-methyl-1,3-thiazol-4-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic acid

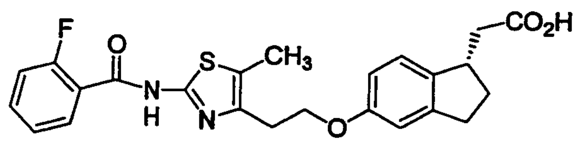


[366] ($C_{24}H_{23}ClN_2O_4S$): LC-MS, RT 3.22 min, $(M+H)^+$ 471.1; ^1H NMR ($DMSO_{d6}$): δ 1.55-1.65 (m, 1H), 2.18-2.28 (m, 2H), 2.30 (s, 3H), 2.58-2.78 (m, 3H), 2.94 (t, 2H), 3.20-3.40 (m, 1H, overlap with water peak), 4.11 (t, 2H), 6.64 (d, 1H), 6.72 (s, 1H), 7.04 (d, 1H), 7.39 (t, 1H), 7.47(t, 1H), 7.51 (d, 1H), 7.54 (d, 1H).

[367]

Example 103

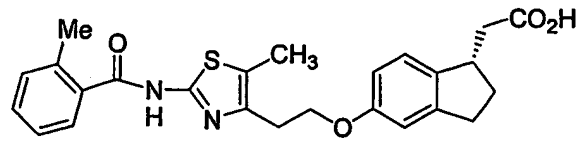
Preparation of [(1*S*)-5-(2-{2-[(2-fluorobenzoyl)amino]-5-methyl-1,3-thiazol-4-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic acid



[368] ($C_{24}H_{23}FN_2O_4S$): LC-MS, RT 3.24 min, $(M+H)^+$ 455.2; ^1H NMR ($DMSO_{d6}$): δ 1.54-1.64 (m, 1H), 2.19-2.25 (m, 2H), 2.29 (s, 3H), 2.58-2.78 (m, 3H), 2.95 (t, 2H), 3.20-2.30 (m, 1H), 4.13 (t, 2H), 6.64 (d, 1H), 6.73 (s, 1H), 7.05 (d, 1H), 7.27 (t, 1H), 7.32 (d, 1H), 7.52-7.60 (m, 1H), 7.66 (t, 1H).

[369] **Example 104**

Preparation of [(1*S*)-5-(2-{5-methyl-2-[(2-methylbenzoyl)amino]-1,3-thiazol-4-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic acid

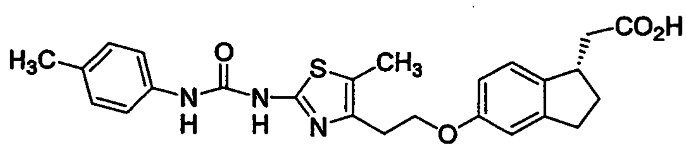


[370] ($C_{25}H_{26}N_2O_4S$): LC-MS, RT 3.28 min, $(M+H)^+$ 451.2; ^1H NMR ($DMSO_{d6}$): δ 1.54-1.64 (m, 1H), 2.19-2.25 (m, 2H), 2.29 (s, 3H), 2.34 (s, 3H), 2.58-2.78 (m, 3H), 2.95 (t, 2H), 3.25-3.32 (m, 1H, overlap with water peak), 4.12 (t, 2H), 6.64 (d, 1H), 6.72 (s, 1H), 7.05 (d, 1H), 7.21-7.27 (m, 2H), 7.36 (t, 1H), 7.46 (d, 1H).

[371] Examples 105 and 106 characterized below, were prepared by a straightforward reaction of Intermediate I with the appropriate isocyanate, followed by hydrolysis following the procedures described for Example 80 and Example 78, Step 2.

[372] **Example 105**

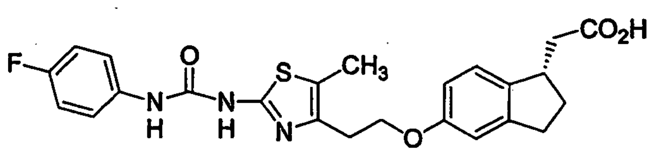
Preparation of ((1*S*)-5-{2-[5-methyl-2-({[(4-methylphenyl)amino]carbonyl}amino)-1,3-thiazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid



[373] ($C_{25}H_{27}N_3O_4S$): LC-MS, RT 3.10 min, $(M+H)^+$ 466.1; ^1H NMR ($CDCl_3$): δ 1.67-1.73 (m, 1H), 2.29 (s, 3H), 2.34 (s, 3H), 2.41-2.89 (m, 5H), 3.15 (t, 2H), 3.40-3.50 (m, 1H), 4.12 (t, 2H), 6.55 (d, 1H), 6.66 (s, 1H), 6.97 (d, 1H), 7.10 (d, 2H), 7.39 (d, 2H).

[374] **Example 106**

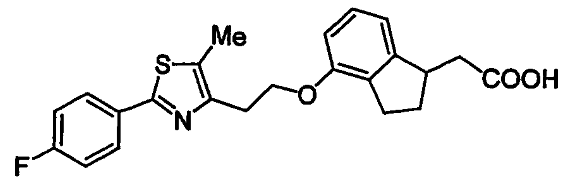
Preparation of ((1*S*)-5-{2-[2-({[(4-fluorophenyl)amino]carbonyl}amino)-5-methyl-1,3-thiazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid



[375] ($C_{24}H_{24}N_3O_4S$): LC-MS, RT 3.11 min, $(M+H)^+$ 470.0; ^1H NMR ($CDCl_3$): δ 1.66-1.74 (m, 1H), 2.33 (s, 3H), 2.35-2.80 (m, 5H), 3.05 (t, 2H), 3.42-3.50 (m, 1H), 4.12 (t, 2H), 6.60 (d, 1H), 6.72 (s, 1H), 6.96 (d, 1H), 7.02 (d, 2H), 7.40-7.48 (m, 2H).

[376] **Example 107**

Preparation of 4-{2-[2-(4-fluorophenyl)-5-methyl-1,3-thiazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid



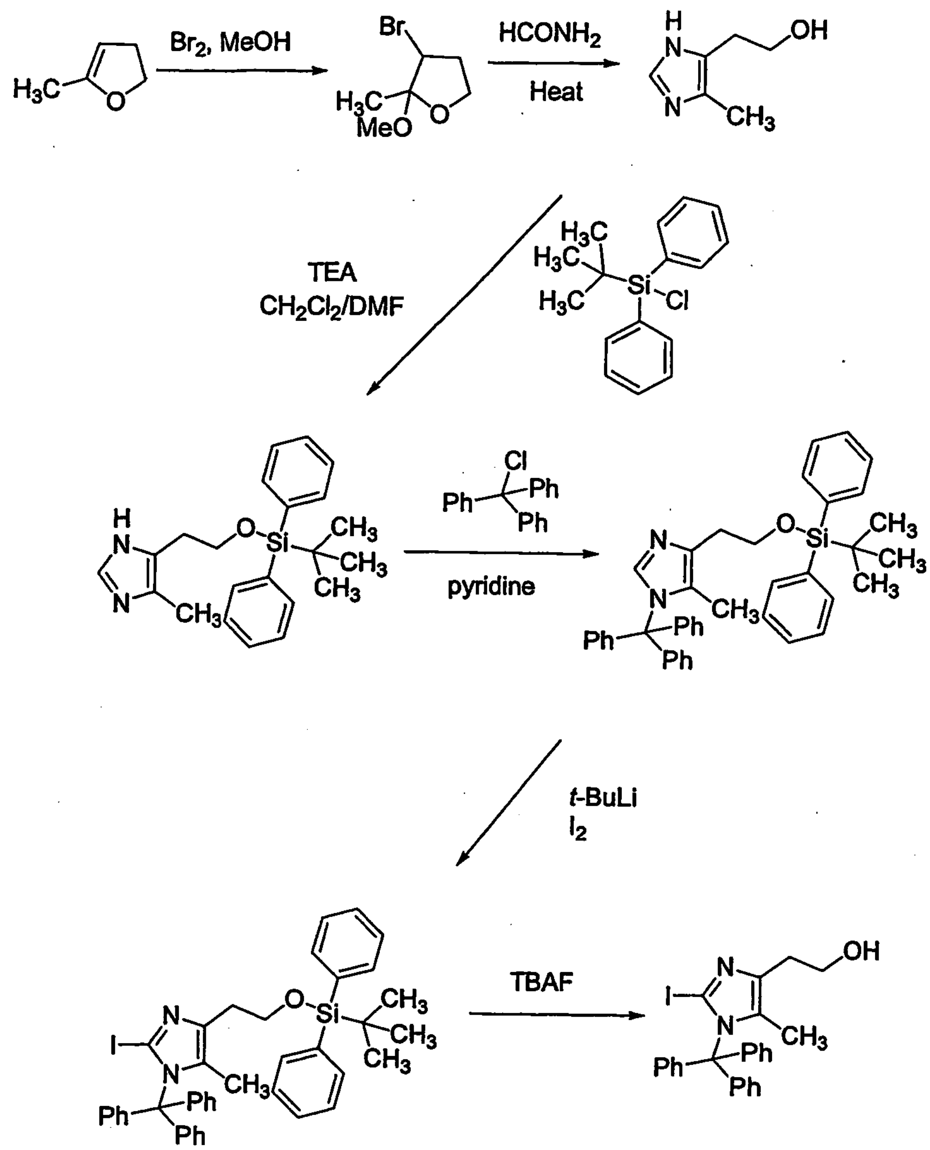
[377] By using the Mitsunobu procedure described for Example 12, Step 5, (Intermediate D, Steps 1, 2 and 6) and 4-methoxy-1-indanone and 2-[2-(4-fluorophenyl)-5-methyl-1,3-thiazol-4-yl]ethanol as starting materials, the title compound was prepared. LC-MS, RT 3.47 min., [M+H]+ = 412.1.

[378] Reaction Schemes 15-21 summarize the synthetic methods utilized for the preparation of compounds of Formula (Ib). These methods were used to prepare Intermediates J, K, and L, and Examples 108-178, as specifically described below.

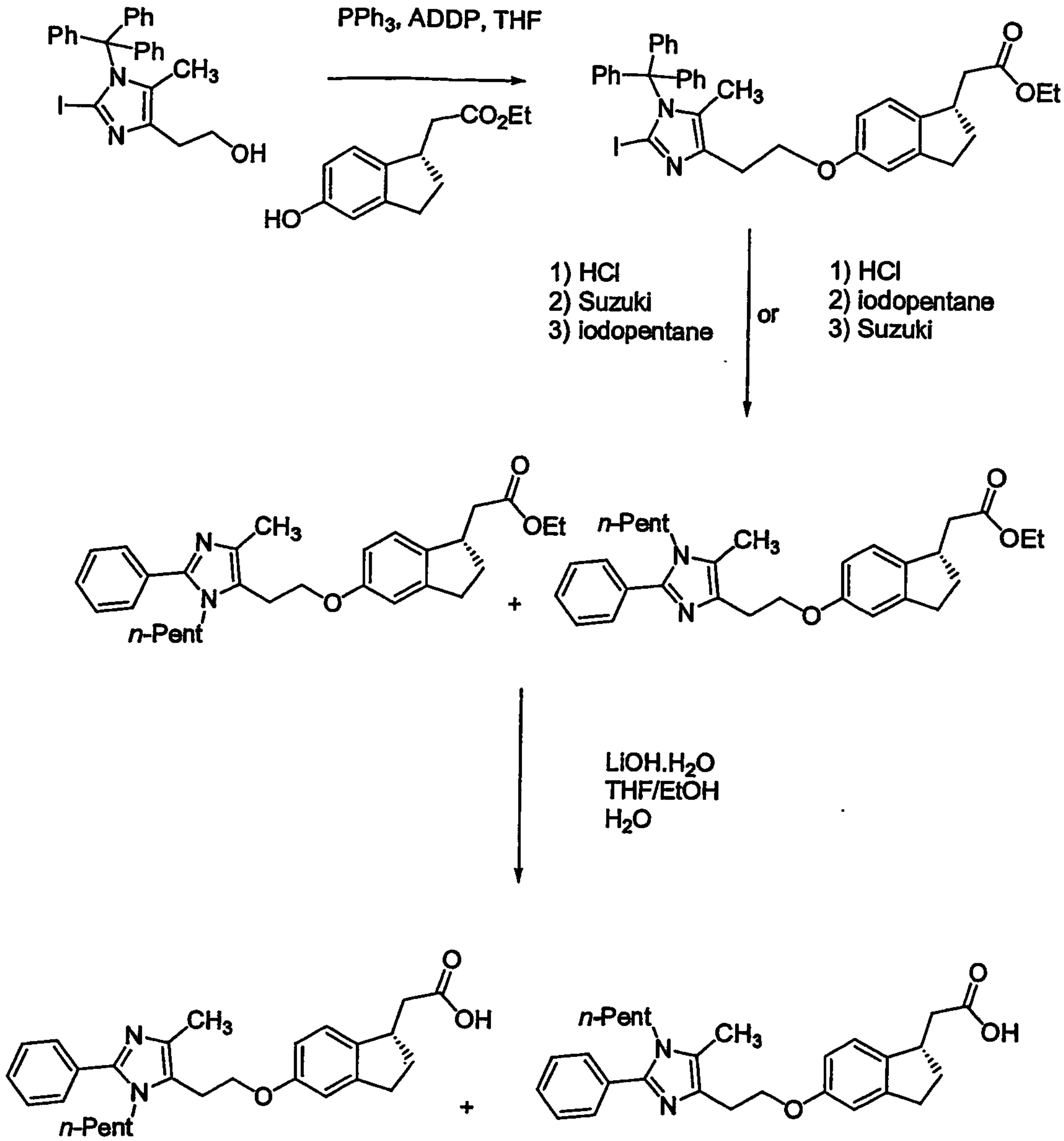
[379]

Preparation of Imidazoles

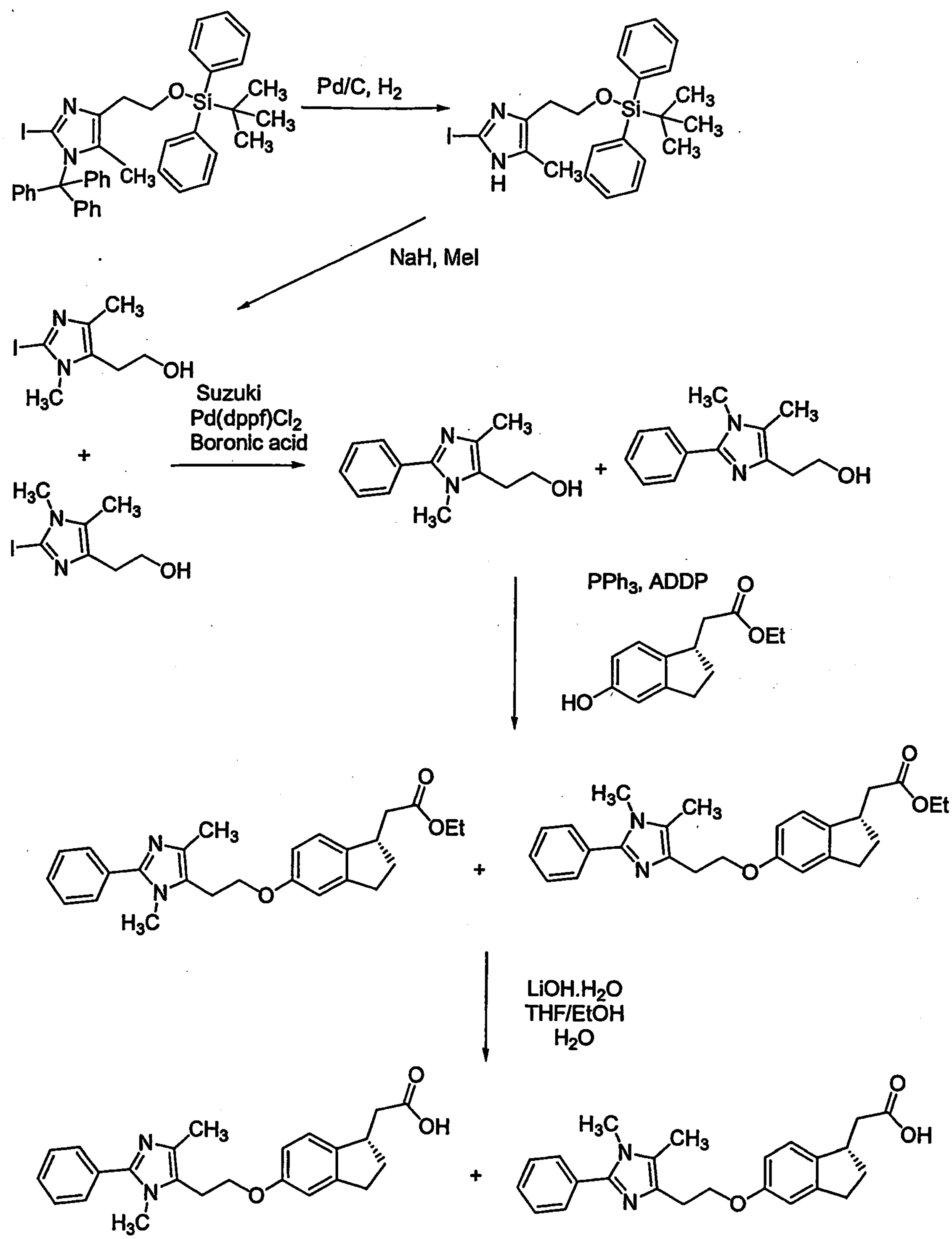
Reaction Scheme 15, Part 1



[380] Reaction Scheme 15, Part 2

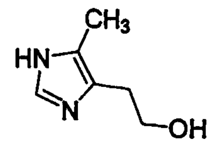


[381] **Reaction Scheme 16**



[382] **Intermediate J**

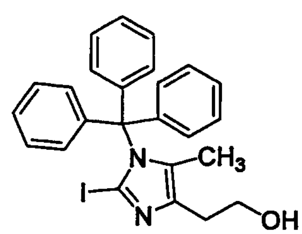
Preparation of 4-(2-hydroxyethyl)-5-methyl-1*H*-imidazole



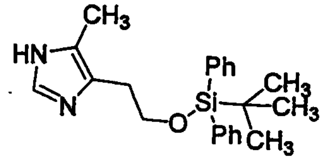
[383] To a solution of 35 g (0.416mol) 4,5-dihydro-2-methylfuran and 38.6 g (0.458 mol) anhydrous sodium acetate in 200 mL methanol, cooled to –60°C in a dry ice-acetone bath, was added dropwise over a duration of 3 h and under vigorous stirring, a pre-cooled solution of 22 mL (0.43 mol) bromine dissolved in 300 mL methanol. The reaction mixture was stirred overnight and the temperature was maintained at about 10°C. The mixture was diluted with 75 mL cold water and extracted with ether/pentane (1:1). The organic layer was washed successively with 1N sodium bicarbonate, 1N sodium sulfite, and brine. The organic layer was dried over magnesium sulfate and concentrated *in vacuo* to afford the bromoketal as a colorless liquid, which was immediately taken to the next step.

[384] The crude mixture from the previous step was immediately refluxed with 250 mL formamide for 6 h. After cooling, the solvent was removed under reduced pressure. The residue was diluted with 500 mL water, and then treated with 200 g Dowex 50W-8X (acid form). The resin was washed successively with water and methanol and the crude base was eluted with 0.5 N ammonia-methanol (15 mL of 58% aqueous ammonia per liter of methanol). The eluant was concentrated *in vacuo* to give 16.35 g (31%) of the desired product. ^{1}H NMR ($CDCl_3$-d_1): δ 2.2 (s, 3H), 2.8 (t, 2H), 3.7 (t, 2H), 8.2 (s, 1H).

[385] **Intermediate K**

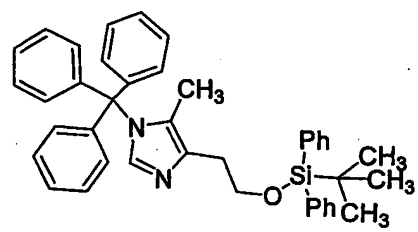


[386] Step 1: Preparation of 4-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-5-methyl-1*H*-imidazole



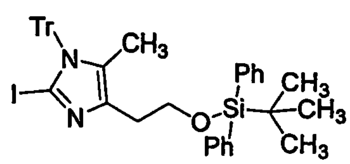
[387] To a solution of 16.35 g (0.130 mol) 4-(2-hydroxyethyl)-5-methyl-1*H*-imidazole (Intermediate A) dissolved in 100 mL DMF was added 53.6 g (0.195 mol) TBDPSCl and 3.17 g DMAP (0.026 mol). The reaction mixture was stirred at 60°C for 18 h. The reaction mixture was cooled to rt and 300 mL water was then added. The solution was extracted with 500 mL of a 1:1 mixture of hexane and diethyl ether. A white solid came out of the solution. The water-DMF layer was removed and the white solid was dissolved in dichloromethane. The dichloromethane layer was washed with water (two times), brine, and then dried over sodium sulfate. The solvent was removed *in vacuo* to give 42.54 g (90% yield) of the product. ^{1}H NMR ($CDCl_3$-d_1): δ 1.5 (s, 9H), 2.1 (s, 3H), 2.8 (t, 2H), 3.4 (t, 2H), 7-7.6 (m, 10H), 8.2 (d, 1H).

[388] Step 2. Preparation of 4-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-5-methyl-1-trityl-1*H*-imidazole



[389] To a solution of 42.5 g (0.117 mol) 4-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-5-methyl-1*H*-imidazole in 100 mL pyridine was added 36 g (0.129 mol) triphenylmethylchloride. The reaction mixture was stirred at 60°C for 16 h. The solvent was evaporated and the residue was mixed with water and extracted with ethyl acetate. The organic layer was washed with brine, and then dried over sodium sulfate. The solvent was removed *in vacuo*, and the residue was purified by column chromatography to give 5.28 g of 4-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-5-methyl-1-trityl-1*H*-imidazole. ^{1}H NMR ($CDCl_3$-d_1): δ 1.1 (s, 9H), 1.4 (s, 3H), 2.8 (t, 2H), 3.9 (t, 2H), 7.1-7.6 (m, 25H), 7.8 (d, 1H).

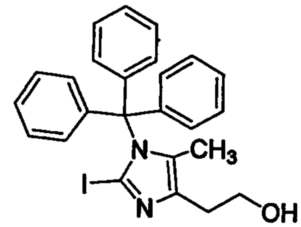
[390] Step 3. Preparation of 4-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-2-iodo-5-methyl-1-trityl-1*H*-imidazole



[391] To a solution of 5.28 g (8.7 mmol) 4-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-5-methyl-1-trityl-1*H*-imidazole in 30 mL THF was added dropwise at –78°C, 4.2 mL (10.4 mmol) *n*-BuLi (2.5 M in hexane). The mixture was stirred for 30 minutes after which 2.21 g (8.7 mmol) of iodine dissolved in THF (20 mL) was added. The reaction mixture was

stirred for 1.5 h at –78°C, and then quenched with methanol. The solvent was removed and the product was purified by column chromatography to give 5.4 g (85% yield) of the title compound. ^{1}H NMR ($CDCl_3$-d_1): δ 1.0 (s, 9H), 1.5 (s, 3H), 2.7 (t, 2H), 4.0 (t, 2H), 7.1-7.6 (m, 25H).

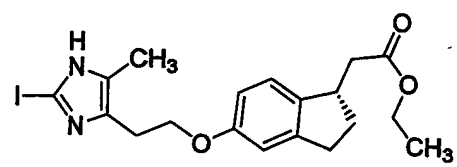
[392] Step 4. Preparation of 2-(2-iodo-5-methyl-1-trityl-1*H*-imidazol-4-yl)ethanol



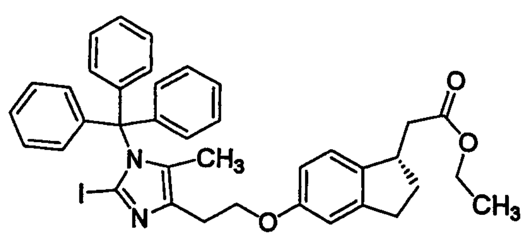
[393] 5-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)-2-iodo-4-methyl-1-trityl-1*H*-imidazole (1.93 g, 2.64 mmol), dissolved in THF (10 mL), was added to 15 mL *tert*-butylammonium fluoride (1 M/THF) and stirred for 20 h. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography with 30% to 50% ethyl acetate in hexanes to afford 1.2 g (2.43 mmol, 92%) of the desired product. ^{1}H NMR ($CDCl_3$-d_1): δ 7.18-7.40 (m, 15 H), 3.88 (t, 2 H), 2.67 (t, 2 H), 1.41 (s, 3 H).

[394] **Example 108**

Preparation of ethyl {(1*S*)-5-[2-(2-iodo-5-methyl-1*H*-imidazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate



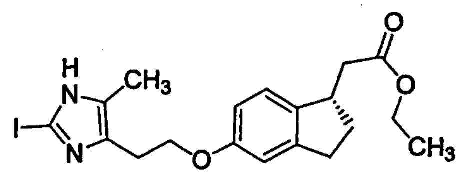
[395] Step 1. Preparation of ethyl {(1*S*)-5-[2-(2-iodo-5-methyl-1-trityl-1*H*-imidazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate



[396] Ethyl ((1*S*)-5-hydroxy-2,3-dihydro-1*H*-inden-1-yl)acetate (Intermediate D, 400 mg, 1.82 mmol), imidazole alcohol (Intermediate K, 900 mg, 1.82 mmol), ADDP (688 mg, 2.73 mmol), and Ph_3P (715 mg, 2.73 mmol) in 30 mL anhydrous THF was stirred at rt under argon for 3 days. The mixture was treated with 7 mL hexanes, and the solid was filtered out. THF was removed under reduced pressure. The crude product was purified by flash

chromatography using 10% ethyl acetate in hexanes to afford 0.58 g (0.83 mmol, 46%) of the title compound. ^{1}H NMR (CDCl$_3$-d_1): δ 7.18-7.40 (m, 15 H), 7.08 (d, 1 H), 6.72 (s, 1 H), 6.65 (d, 1 H), 4.05-4.21 (m, 4 H), 3.42-3.59 (m, 1 H), 2.65-2.97 (m, 5 H), 2.30-2.42 (m, 2 H), 1.65-1.81 (m, 1 H), 1.50 (s, 3 H), 0.85 (t, 3 H).

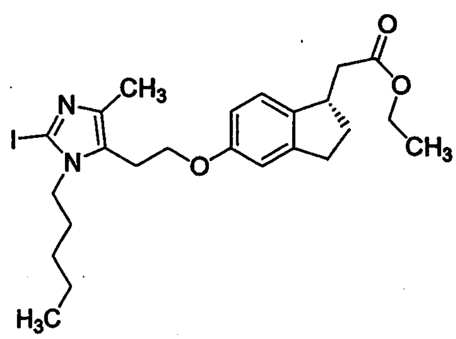
[397] Step 2. Preparation of ethyl {(1*S*)-5-[2-(2-iodo-5-methyl-1*H*-imidazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate



[398] Ethyl {(1*S*)-5-[2-(2-iodo-5-methyl—trityl-1*H*-imidazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate (the product of Step 1, 546 mg, 0.81 mmol) was dissolved in ethanol (5 mL) followed by addition of 1 mL of 1N HCl, and the reaction mixture was stirred for 16 h. The reaction was monitored by LCMS. After the completion of the reaction, the reaction mixture was concentrated under reduced pressure leaving a solid, which was used for the preparation of Example 109 and Example 110 without purification.

[399] **Example 109**

Preparation of ethyl (1*S*)-5-{2-[2-(4-methoxyphenyl)-4-methyl-1-pentyl-1*H*-imidazol-5-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetate

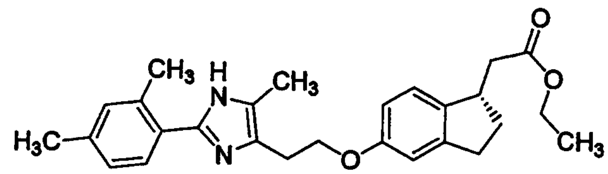


[400] To a solution of ethyl {(1*S*)-5-[2-(2-iodo-5-methyl-1*H*-imidazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate (Example 108, 186 mg) in DMF (10 mL) was added potassium carbonate and iodopentane (64 μL), and the mixture was heated up to 80°C for 16 h. The mixture was then cooled to rt, diluted with water, and extracted with ethyl acetate (30 mL x 3). The organic layer was washed with water, brine, dried over sodium sulfate, and concentrated under reduced pressure to afford an oil. Purification by flash chromatography with 10% to 20% ethyl acetate in hexanes afforded 28 mg of the desired product, ethyl ((1S)-5-{2-[2-(4-methoxyphenyl)-4-methyl-1-pentyl-1*H*-imidazol-5-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetate, and 80 mg of its regioisomer, ethyl {(1*S*)-5-

[2-(2-iodo-5-methyl-1-pentyl-1*H*-imidazole-4-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl) acetate. ^{1}H NMR (desired product): ($CDCl_3$-d_1): δ 7.09 (d, 1 H), 6.68 (s, 1 H), 6.62 (d, 1 H), 4.05-4.21 (m, 4 H), 3.84-3.96 (t 2H), 3.48-3.55 (m, 1 H), 3.08 (t, 2 H), 2.78-2.92 (m, 2 H), 2.71 (dd, 1 H), 2.35-2.46 (m, 2 H), 2.32 (s, 3 H), 1.72-1.88 (m, 3 H), 1.32-1.44 (m, 4 H), 1.28 (t, 3 H), 0.95 (t, 3 H).

[401] **Example 110**

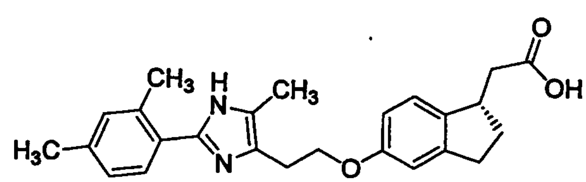
Preparation of ethyl ((1*S*)-5-{2-[2-(2,4-dimethylphenyl)-5-methyl-1*H*-imidazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetate



[402] To a mixture of 2,4-dimethylphenylboronic acid (33 mg, 0.22 mmol), ethyl {(1*S*)-5-[2-(2-iodo-5-methyl-1*H*-imidazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl acetate (Example 108, 25 mg, 0.06 mmol) and [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (5 mg) was added toluene (0.8 mL) and dioxane (0.2 mL). The resulting solution was degassed under argon for half an hour, followed by addition of sodium bicarbonate solution (2 M, 0.2 mL), and then heated up to 85°C for 48 h. The reaction mixture was allowed to cool to rt. The solvent was removed under reduced pressure, and the crude product was carried on for use in the preparation of Example 111 without purification. MS (ES) 433.3; HPLC RT 2.69 min.

[403] **Example 111**

Preparation of ((1*S*)-5-{2-[2-(2,4-dimethylphenyl)-5-methyl-1*H*-imidazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid

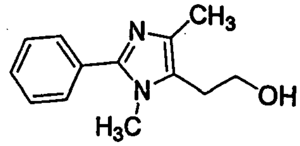


[404] To a solution of ethyl ((1*S*)-5-{2-[2-(2,4-dimethylphenyl)-5-methyl-1*H*-imidazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetate (crude product from Example 110) in ethanol was added lithium hydroxide (42 mg, 1 mmol), and the mixture was heated to 40°C for 1 h. The reaction mixture was then allowed to cool to rt and the pH of the solution was adjusted to 5 using 0.5N HCl. The solution was evaporated under reduced pressure and the crude product was subjected to HPLC purification with gradient elution from 0% acetonitrile in water to 70% acetonitrile in water to afford 12.8 mg of the title compound.

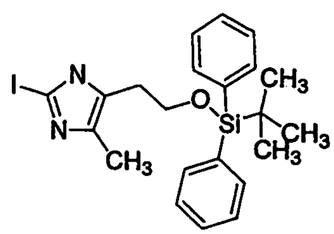
^{1}H NMR ($CDCl_3$): δ 7.38 (d, 1 H 7.30 (s, 1 H), 7.24 (d, 1 H), 7.11 (d, 1 H), 6.80 (s, 1 H), 6.72 (d, 1 H), 4.21 (t, 2 H), 3.38-3.52 (m, 1 H), 3.18 (t, 2 H), 2.71-2.92 (m, 2 H),2.68 (dd, 1 H), 2.28-2.41 (m, 11 H), 1.64-1.80 (m, 1 H), MS (ES) 405; HPLC RT 2.22 min.

[405] Intermediate L

Preparation of 2-(1,4-dimethyl-2-phenyl-1*H*-imidazol-5-yl)ethanol

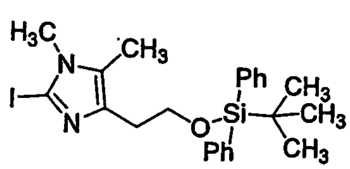


[406] Step 1. Preparation of 5-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-2-iodo-4-methyl-1*H*-imidazole

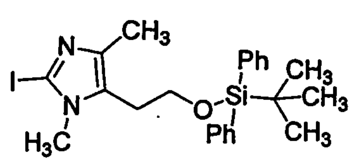


[407] A dried 100 mL round bottom flask was charged with 118 mg of Pd/C catalyst. The flask was flushed with argon, and then the catalyst was wet with ethanol (1 mL) followed by addition of 4-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-2-iodo-5-methyl-1-trityl-1*H*-imidazole (product from Step 3, Intermediate K, 1.18 g, 1.61 mmol) in ethanol (20 mL). HCl (1N, 0.5 mL) was added to the mixture, the flask was fitted with a hydrogen balloon, and the mixture was then stirred at rt for 28 h. The mixture was filtered through a Celite® plug, which was then eluted with ethyl acetate (100 mL). The combined solvents were then removed under reduced pressure. The crude product was treated with 5 mL dichloromethane, and the suspension solid was filtered to afford 535 mg (68%) of the desired product. ^{1}H NMR ($CDCl_3$-d_1): δ 7.51 (d, 4 H), 7.26-7.40 (m, 6 H), 3.78 (t, 2 H), 2.68 (t, 2 H), 2.06 (s, 3 H), 0.98 (s, 9 H).

[408] Step 2. Preparation of 5-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-2-iodo-1,4-dimethyl-1*H*-imidazole and 4-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-2-iodo-1,5-dimethyl-1*H*-imidazole.



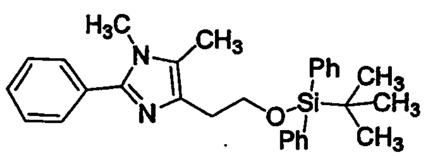
Isomer A



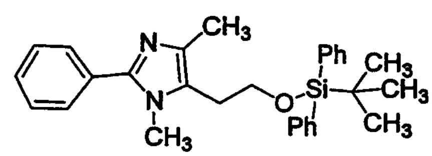
Isomer B

[409] To a solution of 5-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-2-iodo-4-methyl-1*H*-imidazole (490 mg, 1 mmol) in *N,N*-dimethylformamide (5 mL) was added sodium hydride (30 mg, 1.2 mmol) in 1 mL DMF, and the reaction mixture was stirred for 30 minutes, followed by addition of methyl iodide (70 μL, 1.1 mmol). The mixture was stirred at rt for 2h before water was added to quench the reaction. The aqueous layer was extracted with ethyl acetate (200 mL), washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give an oil. The crude product was then purified by flash chromatography with 5% to 20% ethyl acetate in hexanes to afford 500 mg of product as a 1 to 2 mixture of two regioisomers: 5-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-2-iodo-1,4-dimethyl-1*H*-imidazole (Isomer A) and 4-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-2-iodo-1,5-dimethyl-1*H*-imidazole (Isomer B). Mixture: ^1H NMR ($CDCl_3$-d_1) δ 7.42-7.56 (m, 4 H), 7.20-7.38 (m, 6 H), 3.78 (3.61, Isomer B) (t, 2 H), 3.32 (3.19, Isomer B) (s, 3H), 2.68 (2.74, isomer B) (t, 2 H), 2.04 (1.99, Isomer B) (s, 3 H), 0.91 (s, 9 H).

[410] <u>Step 3. Preparation of 4-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-1,5-dimethyl-2-phenyl-1*H*-imidazole (Isomer A) and 5-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-1,4-dimethyl-2-phenyl-1*H*-imidazole (Isomer B)</u>



Isomer A

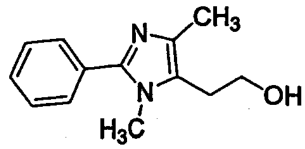


Isomer B

[411] To a mixture of phenylboronic acid (73 mg, 0.6 mmol), the mixture of the two regioisomers 5-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-2-iodo-1,4-dimethyl-1*H*-imidazole and 4-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-2-iodo-1,5-dimethyl-1*H*-imidazole (from Step 2, 149 mg, 0.3 mmol) and [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (25 mg) was added toluene (4 mL) and dioxane (1 mL). The resulting solution was degassed under argon for half an hour, followed by addition of sodium bicarbonate solution (2 M, 1 mL), and then heated up to 85°C for 48 h. The reaction mixture was allowed to cool to rt. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography with 5% to 10% ethyl acetate in hexanes to afford 26 mg of 4-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-1,5-dimethyl-2-phenyl-1*H*-imidazole (Isomer A): ^1H NMR ($CDCl_3$-d_1): δ 7.18-7.80 (m, 15 H), 3.86 (t, 2 H), 3.42 (s, 3 H), 2.86 (t, 2 H), 2.02 (s, 3 H), 1.01 (s, 9 H). Also isolated was

20 mg of 5-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-1,4-dimethyl-2-phenyl-1*H*-imidazole (Isomer B): ^{1}H NMR ($CDCl_3$-d_1): δ 7.60 (d, 4 H), 7.52 (d, 2 H), 7.31-7.46 (m, 9 H), 3.78 (t, 2 H), 3.40 (s, 3 H), 2.82 (t, 2 H), 2.14 (s, 3 H), 1.02 (s, 9 H).

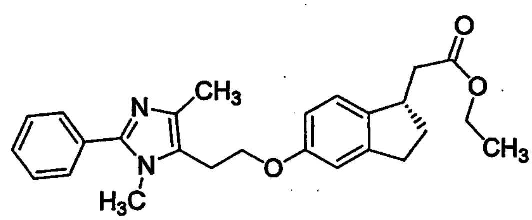
[412] Step 4. Preparation of 2-(1,4-dimethyl-2-phenyl-1*H*-imidazol-5-yl)ethanol



[413] To solution of 5-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-1,4-dimethyl-2-phenyl-1*H*-imidazole (from Step 3, 20 mg) in methanol (10 mL) was added sodium hydroxide (20 mg, 0.5 mmol). The reaction mixture was then heated up to 66°C overnight. After methanol was removed, the crude product was diluted with ether and water. The water layer was extracted with ether (20 mL) twice. The combined organic layer was dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography to afford 8 mg of desired product. ^{1}H NMR ($CDCl_3$-d_1): δ 7.42 (d, 2 H), 7.21-7.38 (m, 3 H), 3.67 (t, 2 H), 3.45 (s, 3 H), 2.76 (t, 2 H), 2.11 (s, 3 H).

[414] **Example 112**

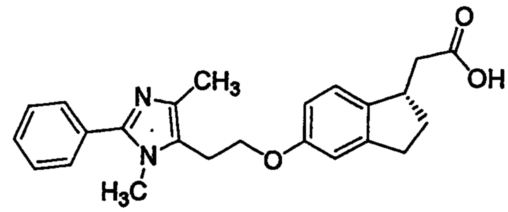
Preparation of ethyl {(1*S*)-6-[2-(1,4-dimethyl-2-phenyl-1*H*-imidazol-5-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate



[415] Ethyl ((1*S*)-5-hydroxy-2,3-dihydro-1*H*-inden-1-yl)acetate (Intermediate D, 7.5 mg, 0.034 mmol), imidazole alcohol (Intermediate L, 8 mg, 1.82 mmol), TMAD, (12 mg, 0.07 mmol), and Ph_3P (18 mg, 0.07 mmol) in 1 mL anhydrous dichloromethane was stirred at rt under argon for 24 h. The mixture was treated with 0.1 mL hexanes, and the solid was filtered out. The solvent was removed under reduced pressure. The crude product was purified by HPLC to afford 13 mg of the title compound. ^{1}H NMR ($CDCl_3$-d_1): δ 7.50-7.68 (m, 5H), 7.08 (d, 1H), 6.71 (s, 1 H), 6.62 (d, 1 H), 4.08-4.22 (m, 4 H), 3.83 (s, 3 H), 3.52 (q, 1 H), 3.14 (t, 2 H), 2.78-2.91 (m, 2 H), 2.70 (dd, 1 H), 2.30-2.48 (m, 5 H), 1.62-1.81 (m, 1 H), 1.16 (t, 3 H); MS (ES) 419.4; HPLC RT 3.11 min.

[416] **Example 113**

Preparation of {(1*S*)-6-[2-(1,4-dimethyl-2-phenyl-1*H*-imidazol-5-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic acid

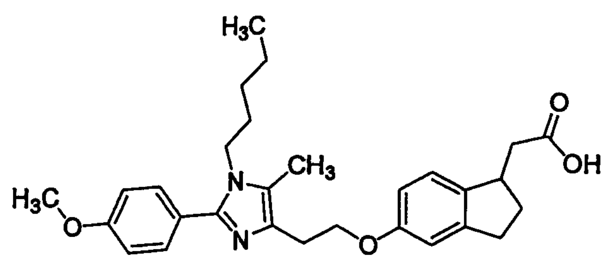


[417] To a solution of ethyl {(1*S*)-6-[2-(1,4-dimethyl-2-phenyl-1*H*-imidazol-5-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate (13 mg, 0.03 mmol) in ethanol was added lithium hydroxide (10 mg), and the mixture was heated to 40°C for 1 h. The reaction mixture was then allowed to cool to rt, and the pH of the solution was adjusted to 5 using 0.5N HCl. The solvent was removed under reduced pressure and the crude product was subjected to HPLC purification with gradient elution from 0% acetonitrile in water to 70% acetonitrile in water to afford 10.5 mg of the title compound. ^{1}H NMR ($CDCl_3$): δ 7.50-7.68 (m, 5 H), 7.09 (d, 1 H), 6.72 (s, 1 H), 6.61 (d, 1 H), 4.18 (t, 2 H), 3.81 (s, 3 H), 3.40-3.58 (m, 1 H), 3.16 (t, 2 H), 2.61-2.92 (m, 3 H), 2.22-2.46 (m, 5 H), 1.65-1.82 (m, 1 H); MS (ES) 391.2; HPLC RT 2.19 min.

[418] Using the procedures described for the preparation of Example 113 and Intermediate L above, and by substituting the appropriate starting materials, Examples 114 and 115 described below and Examples 116-130, summarized in Table 7, were similarly prepared.

[419] **Example 114**

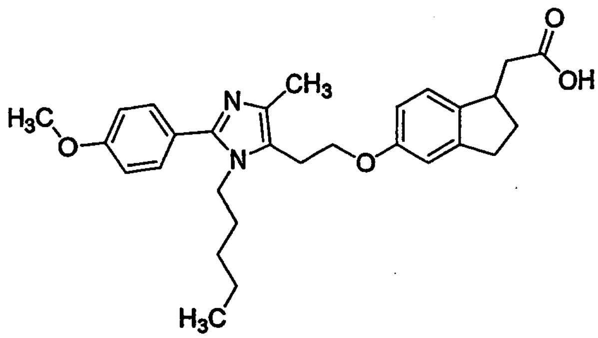
Preparation of (5-{2-[5-methyl-2-(4-methoxyphenyl)-1-pentyl-1*H*-imidazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid



[420] ^{1}H NMR ($CDCl_3$): δ 7.46 (d, 2 H), 7.04 (d, 3 H), 6.75 (s, 1 H), 6.62 (d, 1 H), 4.21 (t, 2 H), 3.96 (t, 2 H), 3.82 (s, 3 H), 3.40-3.54 (m, 1 H), 3.18 (t, 2 H), 2.70-2.92 (m, 3 H), 2.30-2.50 (m, 5 H), 1.61-1.80 (m, 3 H), 1.16-1.34 (m, 4 H), 0.85 (t, 3 H); MS (ES) 477.5; HPLC RT 2.59 min.

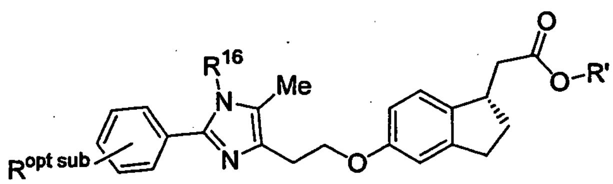
[421] **Example 115**

Preparation of 5-{2-[2-(4-methoxyphenyl)-4-methyl-1-pentyl-1*H*-imidazol-5-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid

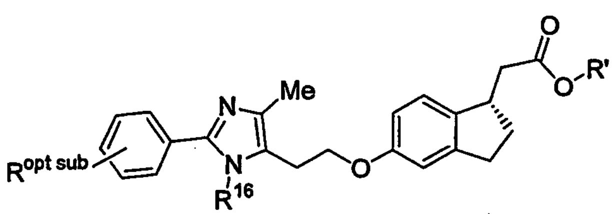


[422] ^{1}H NMR ($CDCl_3$): δ 7.46 (d, 2 H), 7.01-7.12 (m, 3 H), 6.70 (s, 1 H), 6.62 (d, 1 H), 4.10-4.21 (m, 4 H), 3.85 (s, 3 H), 3.41-3.58 (m, 1 H), 3.11 (t, 2 H), 2.66-2.95 (m, 3 H), 2.30-2.48 (m, 5 H), 1.60-1.82 (m, 3 H), 1.18-1.32 (m, 4 H), 0.89 (t, 3H); MS (ES) 477.6; HPLC RT 2.63 min.

[423] **Table 7**



(III)



(IV)

Example No.	R'	R^{16}	$R^{opt\ sub}$	Isomer	HPLC RT (min)	EI-MS [M+H]+
116	H	$PhCH_2$	H	III and IV (mixture)	2.5	467.3
117	H	$PhCH_2$	H	III	2.52	467.3
118	H	$PhCH_2$	4-MeS-	III	2.64	513.4
119	H	$PhCH_2$	3-NO_2	III	2.54	512.3
120	Et	H	4-MeO-	III	2.59	435.3

Example No.	R'	R^{16}	$R^{opt\ sub}$	Isomer	HPLC RT (min)	EI-MS [M+H]+
121	H	*n*-Pent	4-Me	III	2.71	461.3
122	H	Me	4-MeO	IV	2.26	421.2
123	H	Me	4-Ph	IV	2.55	467.3
124	H	Me	4-Et	IV	2.42	419.3
125	Et	Me	4-Ph	IV	2.83	495.4
126	Et	Me	4-Et	III	3.34	447.4
127	H	Me	H	III	2.13	391.2
128	H	Me	4-Et	III	2.37	419.2
129	H	Me	4-Ph	III	2.54	467.3
130	H	Me	4-MeO	III	2.21	421.2

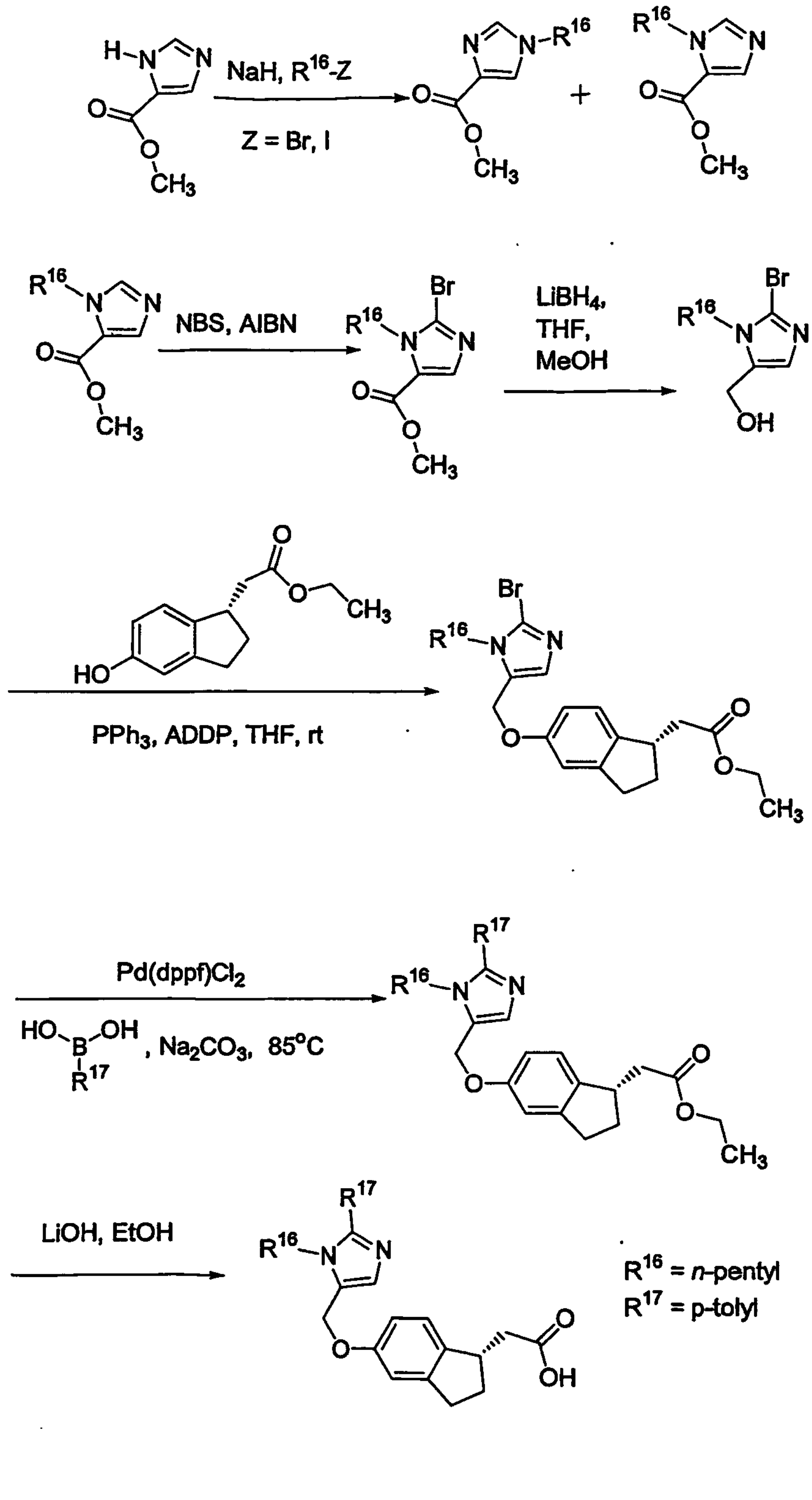
[424] **Table 8**

Example No.	IUPAC name
116	{(1*S*)-5-[2-(1-Benzyl-5-methyl-2-phenyl-1*H*-imidazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}aceticacid; {(1*S*)-5-[2-(1-benzyl-4-methyl-2-phenyl-1*H*-imidazol-5-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic acid
117	{(1*S*)-5-[2-(1-Benzyl-5-methyl-2-phenyl-1*H*-imidazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic acid
118	[(1*S*)-5-(2-{1-Benzyl-5-methyl-2-[4-(methylsulfanyl)phenyl]-1*H*-imidazol-4-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic acid
119	[(1*S*)-5-(2-{1-Benzyl-2-[3-nitrophenyl]-5-methyl-1*H*-imidazol-4-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic acid
120	Ethyl ((1*S*)-5-{2-[2-(4-methoxyphenyl)-5-methyl-1*H*-imidazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetate
121	((1*S*)-5-{2-[5-Methyl-2-(4-methylphenyl)-1-pentyl-1*H*-imidazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid
122	((1*S*)-5-{2-[2-(4-Methoxyphenyl)-1,4-dimethyl-1*H*-imidazol-5-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid
123	((1*S*)-5-{2-[2-(1,1'-Biphenyl-4-yl)-1,4-dimethyl-1*H*-imidazol-5-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid

Example No.	IUPAC name
124	((1*S*)-5-{2-[2-(4-Ethylphenyl)-1,4-dimethyl-1*H*-imidazol-5-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid
125	Ethyl ((1*S*)-5-{2-[2-(1,1'-biphenyl-4-yl)-1,4-dimethyl-1*H*-imidazol-5-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetate
126	Ethyl ((1*S*)-5-{2-[2-(4-ethylphenyl)-1,5-dimethyl-1*H*-imidazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetate
127	{(1*S*)-5-[2-(1,5-Dimethyl-2-phenyl-1*H*-imidazol-4-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic acid
128	((1*S*)-5-{2-[2-(4-Ethylphenyl)-1,5-dimethyl-1*H*-imidazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid
129	((1*S*)-5-{2-[2-(1,1'-Biphenyl-4-yl)-1,5-dimethyl-1*H*-imidazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid
130	((1*S*)-5-{2-[2-(4-Methoxyphenyl)-1,5-dimethyl-1*H*-imidazol-4-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid

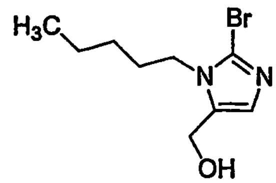
[425] Reaction Scheme 17 summarizes the steps utilized for the preparation of Intermediate M, Example 131, and Example 132.

[426] **Reaction Scheme 17**

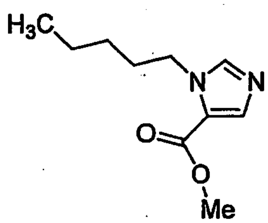


[427] **Intermediate M**

Preparation of (2-bromo-1-pentyl-1*H*-imidazol-5-yl)methanol

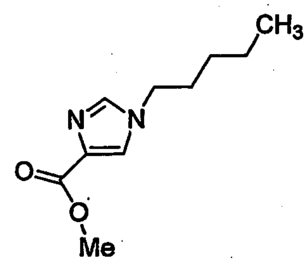


[428] Step 1. Preparation of methyl 1-pentyl-1*H*-imidazole 5-carboxylate (1) and methyl 1-pentyl-1*H*-imidazole 4-carboxylate (2)



(1)

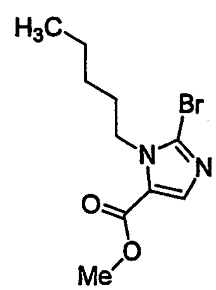
and



(2)

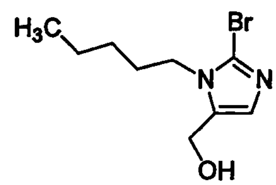
[429] To a solution containing NaH (2.2 g, 44 mmol) in THF (30 mL) at 0°C was added a solution of methyl 1*H*-imidazole 5-carboxylate (10 g, 40 mmol) in THF/DMF (25 mL/30 mL) dropwise. The mixture was warmed to 23°C and stirred for 1 h, and then a solution containing 1-iodopentane (11.5 mL, 44 mmol) in THF (5 mL) was added. The reaction mixture was stirred at 23 °C for 12 h. It was diluted with ethyl acetate (150 mL x 3), extracted with water and saturated sodium bicarbonate, and dried with sodium sulfate. The resulting solution was concentrated *in vacuo* and the residue was purified by flash chromatography (10-50% ethyl acetate in hexanes) to obtain methyl 1-pentyl-1*H*-imidazole 5-carboxylate (1) (2 g, 13%) and methyl 1-pentyl-1*H*-imidazole 4-carboxylate (2) (9.8 g, 63%). Methyl 1-pentyl-1*H*-imidazole 5-carboxylate (1): MS (electrospray) 197.2 $(M+H)^+$, ^1H NMR ($CDCl_3$): δ 0.88 (t, 3H), 1.30 (m, 4H), 1.78 (m, 2H), 3.85 (s, 3H), 4.30 (t, 2H), 7.74 (s, 1H), 7.78 (s, 1H). Methyl 1-pentyl-1*H*-imidazole 4-carboxylate (2): MS (electrospray) 197.1 $(M+H)^+$, ^1H NMR ($CDCl_3$) δ 0.89 (t, 3H), 1.31 (m, 4H), 1.81 (m, 2H), 3.89 (s, 3H), 3.96 (t, 2H), 7.62 (s, 1H), 7.71 (s, 1H).

[430] Step 2. Preparation of methyl 2-bromo-1-pentyl-1*H*-imidazole-5-carboxylate



[431] To a solution of methyl 1-pentyl-1*H*-imidazole 5-carboxylate (2 g, 10 mmol) in CCl_4 (200 mL) was added NBS (3.63 g, 20 mmol), and AIBN (0.084 g, 0.5 mmol). The mixture was heated to 60°C for 16 h with stirring. The mixture was cooled, the solids were removed by filtration, and concentrated under vacuum. The residue was purified by flash chromatography (20%-70% ethyl acetate in hexanes) to obtain the desired product (2 g, 79%). MS (electrospray) 275.1 $(M+H)^+$, ^1H NMR ($CDCl_3$): δ 0.90 (t, 3H), 1.33 (m, 4H), 1.71 (m, 2H), 3.85 (s, 3H), 4.33 (t, 2H), 7.69 (s, 1H).

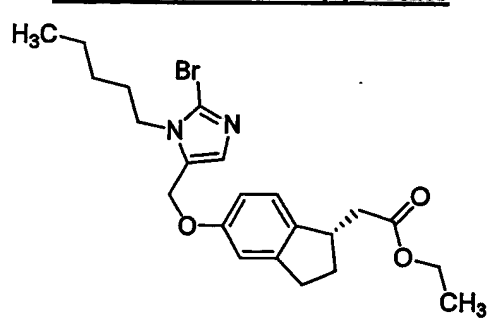
[432] Step 3. Preparation of (2-bromo-1-pentyl-1*H*-imidazol-5-yl)methanol



[433] To a solution of methyl 2-bromo-1-pentyl-1*H*-imidazole-5-carboxylate (1.5 g, 5.1 mmol) in THF (15 mL) was added with MeOH (0.25 mL), $LiBH_4$ (0.25 g, 11.4 mmol), and a drop of water. The reaction was stirred for 16 h. Water was added to the reaction mixture and the pH was adjusted to 6 by addition of 1N HCl. The mixture was extracted with EtOAc and the organic layer was dried with sodium sulfate. Solvents were evaporated under vacuum and the residue was purified by flash chromatography (20% to 60% EtOAc in hexanes) to obtain the title compound in 37% yield (400 mg, 1.6 mmol). MS (electrospray) 247.1 $(M+H)^+$, ^1H NMR ($CDCl_3$): δ 0.92 (t, 3H), 1.31 (m, 4H), 1.72 (m, 2H), 3.95 (t, 2H), 4.59 (s, 2H), 6.88 (s, 1H).

[434] **Example 131**

Preparation of ethyl {(1*S*)-5-[(2-bromo-1-pentyl-1*H*-imidazol-5-yl)methoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate

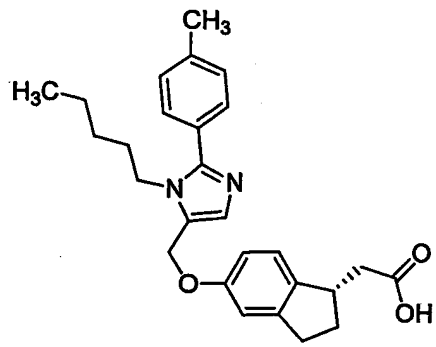


[435] To a solution of (2-bromo-1-pentyl-1*H*-imidazol-5-yl) methanol (Intermediate M, 380 mg, 1.3 mmol) in THF was added with ethyl [(1*S*)-5-hydroxy-2,3-dihydro-1*H*-inden-1-yl]acetate (Intermediate D, 285 mg, 1.3 mmol), ADDP (651 mg, 2.6 mmol), and triphenylphosphine (677 mg, 2.6 mmol). The solution was stirred at rt for 72 h. The

solution was filtered through a silica gel plug, and the filtrate was evaporated under vacuum. The residue was purified by flash chromatography (10 – 30% EtOAc in hexanes) to obtain the title compound in 38% yield (245 mg, 0.5 mmol). MS (electrospray) 451.1 $(M+2)^+$, ^1H NMR ($CDCl_3$): δ 0.89 (t, 3H), 1.31 (m, 7H), 1.77 (m, 3H), 2.40 (m, 2H), 2.73 (m, 1H), 2.88 (m, 2H), 3.52 (m,1H), 3.94 (t, 2H), 4.17 (q, 2H), 4.93 (s, 2H), 6.74 (m, 1H), 6.81 (s, 1H), 7.05 (s, 1H), 7.09 (d, 1H).

[436] **Example 132**

Preparation of {(1*S*)-5-[(1-pentyl-2-phenyl-1*H*-imidazol-5-yl)methoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic acid

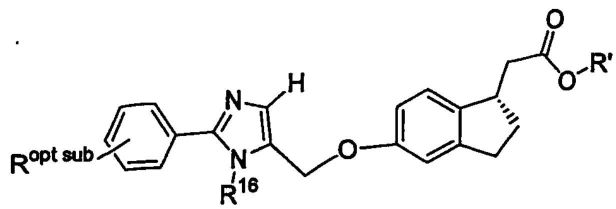


[437] To a solution containing ethyl {(1*S*)-5-[(2-bromo-1-pentyl-1*H*-imidazol-5-yl)methoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate (0.035g, 0.08 mmol), Pd(dppf)Cl_2 (6.3 mg, 10% mol), and 4-methylphenyl boronic acid (0.021g, 0.16 mmol) in degassed toluene and dioxane (4:1, 2 mL) was added aqueous 2 M sodium carbonate (0.5 mL). The mixture was heated to 85°C for 12 h. Solvents were removed under vacuum, and the residue was dissolved in EtOH/water (1:1, 2 mL) and treated with LiOH (0.016 mg, 0.4 mmol). The solution was heated at 50°C for 12 h. Solvents were evaporated under vacuum, and the residue was dissolved in water and adjusted the pH to 5 with 1N HCl. Solvents were evaporated and the residue was dissolved in acetonitrile and purified by HPLC to obtain the desired product in 15% yield (5 mg, 0.01 mmol). MS (electrospray) 433.2 $(M+H)^+$, HPLC RT 2.68 ^1H NMR ($CDCl_3$): δ 0.81 (t, 3H), 1.20 (m, 4H), 1.78 (m, 3H), 2.46 (m, 5H), 2.84 (m, 3H), 3.55 (m, 1H), 4.19 (m, 2H), 5.08 (s, 2H), 6.74 (m, 1H), 6.83 (s, 1H), 7.16 (m, 1H), 7.39 (m, 2H), 7.53 (m, 2H), 7.66 (s, 1H).

[438] Using the methods described above for Intermediate M and Examples 131 and 132, and substituting the appropriate starting materials, the compounds shown in Table 9 below were similarly prepared.

[439]

Table 9



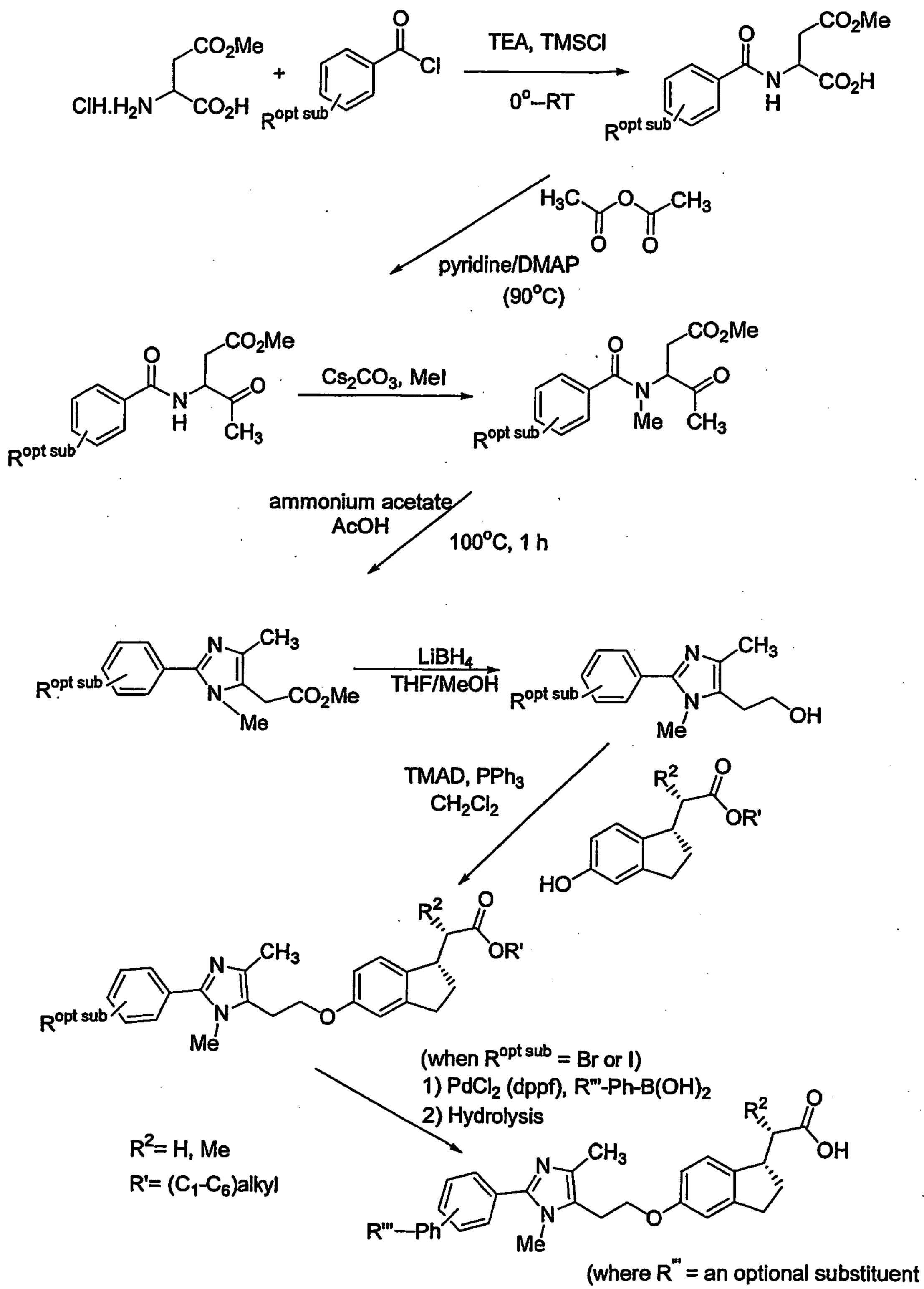
Example No.	R'	R^{16}	$R^{opt\ sub}$	HPLC RT (min)	MS EI[M+H]+
133	H	*n*-Pent	4-MeO-	2.6	449.2
134	H	*n*-Pent	4-CF_3	2.76	487.2
135	H	*n*-Pent	3,4-methylenedioxy	2.6	463.2
136	H	*n*-Pent	3,4-diMe	2.84	447.2
137	H	*n*-Pent	4-(pyrid-4-yl)-	2.38	343.2

[440]

Table 10

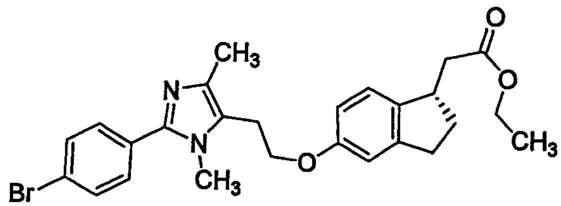
Example No.	IUPAC Name
133	((1S)-5-{[2-(4-Methoxyphenyl)-1-pentyl-1H-imidazol-5-yl]methoxy}-2,3-dihydro-1H-inden-1-yl)acetic acid
134	[(1S)-5-({1-Pentyl-2-[4-(trifluoromethyl)phenyl]-1H-imidazol-5-yl}methoxy)-2,3-dihydro-1H-inden-1-yl]acetic acid
135	((1S)-5-{[2-(1,3-Benzodioxol-5-yl)-1-pentyl-1H-imidazol-5-yl]methoxy}-2,3-dihydro-1H-inden-1-yl)acetic acid
136	((1S)-5-{[2-(3,4-Dimethylphenyl)-1-pentyl-1H-imidazol-5-yl]methoxy}-2,3-dihydro-1H-inden-1-yl)acetic acid
137	((1S)-5-{[1-Pentyl-2-(4-pyridinyl)-1H-imidazol-5-yl]methoxy}-2,3-dihydro-1H-inden-1-yl)acetic acid

[441] **Reaction Scheme 18**

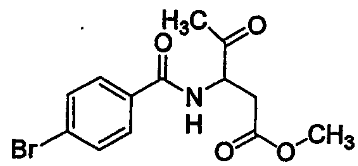


[442] **Example 138**

Preparation of ethyl ((1*S*)-5-{2-[2-(4-bromophenyl)-1,4-dimethyl-1*H*-imidazol-5-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetate

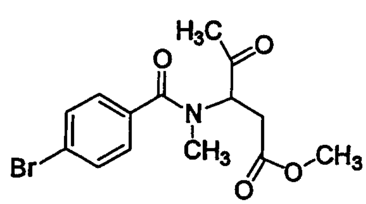


[443] Step 1: Preparation of methyl 3-[(4-bromobenzoyl)amino]-4-oxopentanoate



[444] To a suspension of L-aspartic acid β-methyl ester hydrochloride (10.2 g, 55.6 mmol) in chilled (< 5°C) dichloromethane (200 mL) was added Et_3N (16.9 g, 166.7 mmol) followed by a slow addition of trimethylsilyl chloride (13.3 g, 108.6 mmol). The mixture was warmed to 25°C and stirred for 1 h, cooled again (< 10°C), and *p*-bromobenzoyl chloride (12.2 g, 55.56 mmol) was added dropwise. The mixture was allowed to warm to ambient temperature slowly and stirred for 16 h. The reaction mixture was then diluted with dichloromethane (500 mL) and washed with 1N HCl (500 mL), brine (500 mL), and dried over Na_2SO_4. The resultant amide product (19.3 g, 95%), a white solid, was obtained after solvent removal and drying under vacuum. It was then dissolved in pyridine (50 mL) and DMAP (36 g) was added. Acetic anhydride (56 mL) was added slowly and then the reaction was heated at 90°C for 2 h. The cooled solution was poured into 200 mL ice water and extracted with 800 mL ethyl acetate. The organic layer was washed with 2N HCl (3 x 200 mL) and sat. sodium bicarbonate solution (3 x 200 mL), dried over $MgSO_4$, and concentrated to afford the title compound as a white solid (13.2 g, 68%).

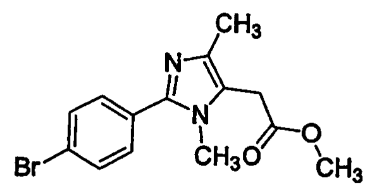
[445] Step 2: Preparation of methyl 3-[(4-bromobenzoyl)(methyl)amino]-4-oxopentanoate



[446] To a solution of the product from Step 1 above (6 g, 18.3 mmol) and cesium carbonate (11.9 g, 36.6 mmol) in N', N'-dimethylformamide (80 mL) was added methyl

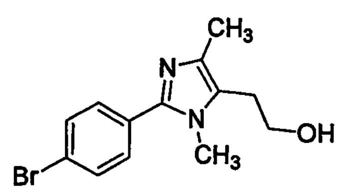
iodide (12.98, 91.4 mmol) at rt over a period of 5 h. The reaction was carefully monitored for 10 h. The crude product was diluted with ethyl acetate (300 mL) and filtered through a Celite® plug with ethyl acetate (300 mL) as eluent. The combined organic solvent was washed with water (3 x 100 mL), brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford a solid crude product, which was used for the next step without purification.

[447] Step 3: Preparation of methyl [2-(4-bromophenyl)-1,4-dimethyl-1*H*-imidazol-5-yl]acetate



[448] Methyl 3-[(4-bromobenzoyl)(methyl)amino]-4-oxopentanoate (1 g, 2.9 mmol) in a dried flask was added acetic acid (50 eq.), ammonium salt (11.3 g, 146.1 mmol), and 50 mL acetic acid (with 1 drop of H_2SO_4), and the flask was heated up to 150°C for 16 h. The reaction mixture was cooled to rt and concentrated under reduced pressure. Cold water (200 mL) was added to the residue and extracted with ethyl acetate (800 mL). The combined organic layer was washed with sat. sodium bicarbonate, brine, dried over Na_2SO_4, and concentrated under reduced pressure gave a crude residue, which was purified by Biotage flash 25 M with 30 to 50% ethyl acetate in hexanes to give 450 mg (48 % yield) of desired product. ^{1}H NMR (300 MHz/ $CDCl_3$) δ 7.72 (d, 2 H), 7.55 (d, 2 H), 3.80 (s, 3 H), 3.74 (s, 3 H), 3.71 (s, 2 H), 2.39 (s, 3 H). EI-LCMS (rel abundance), m/z 323.3 (MH+, 100%).

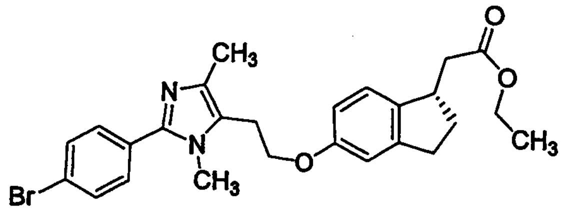
[449] Step 4: Preparation of 2-[2-(4-bromophenyl)-1,4-dimethyl-1*H*-imidazol-5-yl]ethanol



[450] Methyl [2-(4-bromophenyl)-1,4-dimethyl-1*H*-imidazol-5-yl]acetate (445 mg, 1.38 mmol) dissolved in tetrahydrofuran (15 mL) was added 0.7 mL lithium borohydride (2 M solution in tetrahydrofuran) dropwise. The reaction mixture was then stirred at rt and monitored by TLC. Two hours later, water was added to quench the reaction and the aqueous layer was extracted with ethyl acetate (400 mL). The combined organic layer was washed with sat. sodium bicarbonate, dried over sodium sulfate, and concentrated under reduced pressure. The crude product was purified by Biotage flash 25M with 40 to

80% ethyl acetate in hexanes to give 200 mg (49.2 % yield) of the desired product. ^{1}H NMR (300 MHz/ $CDCl_3$) δ 7.52 (d, 2 H), 7.39 (d, 2 H), 3.74 (t, 2 H), 3.53 (s, 3 H), 2.81 (t, 2 H), 2.58 (br, 1 H), 2.178 (s, 3 H). EI-LCMS(rel abundance), m/z 297.2 (MH+, 100%).

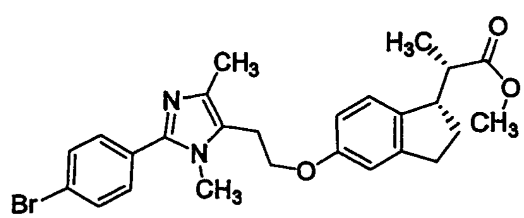
[451] Step 5. Preparation of ethyl ((1*S*)-5-{2-[2-(4-bromophenyl)-1,4-dimethyl-1*H*-imidazol-5-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetate



[452] A suspension of the ethyl [(1*S*)-5-hydroxy-2,3-dihydro-1*H*-inden-1-yl]acetate (Intermediate D, 149.2 mg, 0.68 mmol), 2-[2-(4-bromophenyl)-1,4-dimethyl-1*H*-imidazol-5-yl]ethanol (product of Step 4 above, 200 mg, 0.68 mmol), TMAD (174.81 mg, 1.02 mmol), and Ph_3P (266.6 mg, 1.02 mmol) in 5.0 mL anhydrous dichloromethane was stirred at rt under argon for 20 h. After solids were removed by filtration, dichloromethane was removed under reduced pressure. The remaining mixture was stirred in 3 mL of 50/50 mixture of EtOAc/hexane for 10 minutes, and more solids were formed and removed by filtration. The filtrate was concentrated under reduced pressure to provide an oil. The crude product was redissolved in methanol and filtered through a C_8-Silica plug before it was subjected to HPLC purification with 10 to 70% acetonitrile in water to give 280 mg (83.1% yield) of desired product. ^{1}H NMR (300 MHz/ CD_3OD) δ 7.84 (d, 2 H), 7.60 (d, 2 H), 7.05 (d, 1H), 6.77 (s, 1 H), 6.69 (d, 1 H), 4.21 (t, 2 H), 4.13 (q, 2 H), 3.85 (s, 3 H), 3.44 (qr, 1 H), 3.26 (t, 2 H), 2.64-2.94 (m, 3 H), 2.40 (s, 3 H), 2.25-2.38 (m, 2 H), 1.67-1.75 (m, 1 H), 1.24 (t, 3 H). EI-LCMS(rel abundance), m/z 497.4 (MH+, 75%).

[453] **Example 139**

Preparation of methyl (2*S*)-2-((1*S*)-5-{2-[2-(4-bromophenyl)-1,4-dimethyl-1*H*-imidazol-5-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)propanoate



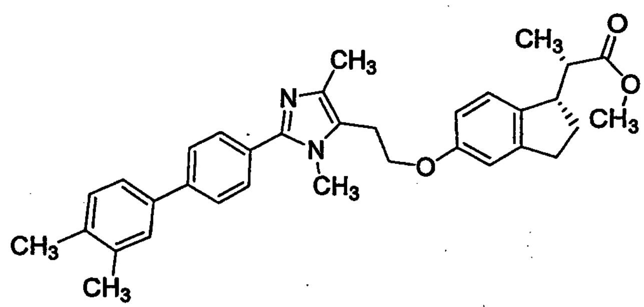
[454] A suspension of the methyl (2*S*)-2-[(1*S*)-5-hydroxy-2,3-dihydro-1*H*-inden-1-yl]propanoate (Intermediate A, 45.5 mg, 0.66 mmol), 2-[2-(4-bromophenyl)-1,4-dimethyl-1*H*-imidazol-5-yl]ethanol (Example 138, Step 4) (195.0 mg, 0.66 mmol), TMAD (170.4 mg, 0.99 mmol), and Ph_3P (260.0 mg, 0.99 mmol) in 5.0 mL anhydrous dichloromethane

was stirred at rt under argon for 20 h. After solids were removed by filtration, dichloromethane was removed under reduced pressure. The remaining mixture was stirred in 3 mL of 50/50 mixture of EtOAc/hexane for 10 minutes, and more solids were formed and removed by filtration. The filtrate was concentrated under reduced pressure to provide an oil. The crude product was redissolved in methanol and filtered through a C_8-Silica plug before it was subjected to HPLC purification with 10 to 70% acetonitrile in water to give 290 mg (88.3 % yield) of desired product. ^{1}H NMR (300 MHz/ CD_3OD) δ 7.81 (d, 2 H), 7.58 (d, 2 H), 6.95 (d, 1H), 6.75 (s, 1 H), 6.68 (d, 1H), 4.20 (t, 2 H), 3.84 (s, 3 H), 3.64 (s, 3 H), 3.40 (q, 1 H), 3.24 (t, 2 H), 2.64-2.90 (m, 3 H), 2.38 (s, 3 H), 2.04-2.16 (m, 1 H), 1.80-1.90 (m, 1 H), 1.00 (d, 3 H). EI-LCMS(rel abundance), m/z 499.3 (MH+, 100%).

[455] **Example 140**

General Method for Suzuki Reaction

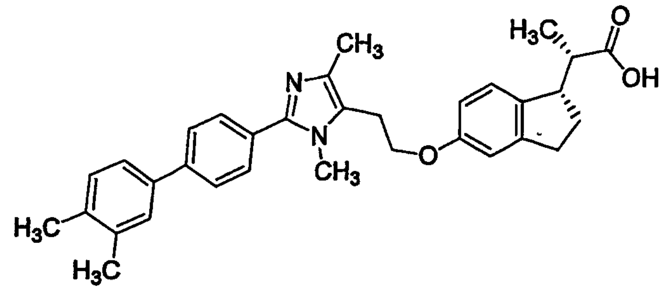
Synthesis of methyl (2*S*)-2-((1*S*)-5-{2-[2-(3',4'-dimethyl-1,1'-biphenyl-4-yl)-1,4-dimethyl-1*H*-imidazol-5-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)propanoate



[456] To a mixture of 3,4-dimethylphenyl boronic acid (17.0 mg, 0.11 mmol), methyl (2*S*)-2-((1*S*)-5-{2-[2-(4-bromophenyl)-1,4-dimethyl-1*H*-imidazol-5-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)propanoate (Example 139, 28 mg, 0.06 mmol), and Pd (dppf)Cl_2 (4.5 mg, 0.006 mmol) was added toluene (2 mL) and dioxane (0.5 mL). The resulting solution was degassed under argon for half an hour, followed by addition of sodium bicarbonate solution (2 M, 0.5 mL), and then heated to 85°C for 16 h. The reaction mixture was allowed to cool to rt and diluted with 10 mL ethyl acetate. The organic layer was separated and passed through a 0.5 g silica plug. The combined organic layer was then concentrated under vacuum, leaving a dark brown oil, which was purified by HPLC with 10 to 80% acetonitrile in water to give 28.2 mg (95.6% yield) of desired product. ^{1}H NMR (CD_3OD) δ 7.90 (d, 2 H), 7.73 (d, 2 H), 7.49 (s, 1 H), 7,43 (d, 1 H), 7.42 (d, 1 H), 6.98 (d, 1 H), 6.79 (s, 1 H), 6.70 (d, 1 H), 4.24 (t, 2 H), 3.91 (s, 3 H), 3.67 (s, 3 H), 3.43 (q, 1 H), 3.28 (t, 2 H), 2.71-2.87 (m, 3 H), 2.36 (s, 3 H), 2.41 (s, 3 H), 2.32 (s, 3 H), 2.09-2.17 (m, 1 H), 1.83-1.93 (m, 1 H), 1.02 (d, 3 H). EI-LCMS(rel abundance), m/z 523.5 (MH+, 75%).

[457] **Example 141**

Preparation of (2*S*)-2-((1*S*)-5-{2-[2-(3',4'-dimethyl-1,1'-biphenyl-4-yl)-1,4-dimethyl-1*H*-imidazol-5-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)propanoic acid

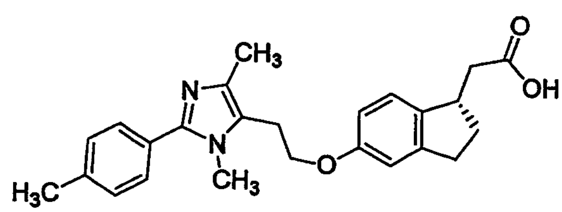


[458] To a solution of methyl (2*S*)-2-((1*S*)-5-{2-[2-(3',4'-dimethyl-1,1'-biphenyl-4-yl)-1,4-dimethyl-1*H*-imidazol-5-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)propanoate (Example 140, 18.2 mg, 0.03 mmol) in ethanol (0.5 mL) and THF (0.5 mL) was added $LiOH{\cdot}H_2O$ (15 mg, 0.35 mmol) followed by addition of 1 mL water. The reaction mixture was then stirred at rt for 4 h. The crude product was then acidified to pH 5-6 and the solvent was removed under reduced pressure, redissolved in methanol, and filtered through a C_8-Silica plug before it was subjected to HPLC purification with 10 to 70% acetonitrile in water to afford desired product 12.7 mg (72% yield). ^{1}H NMR (300 MHz/ CD_3OD) δ 7.89 (d, 2 H), 7.73 (d, 2 H), 7.49 (s, 1 H), 7.43 (d, 1 H), 7.25 (d, 1 H), 7.07 (d, 1 H), 6.78 (s, 1 H), 6.71 (d, 1 H), 4.24 (t, 2 H), 3.90 (s, 3 H), 3.47 (q, 1 H), 3.28 (t, 2 H), 2.67-2.88 (m, 3 H), 2.41 (s, 3 H), 2.53 (s, 3 H), 2.32 (s, 3 H), 2.11-2.18 (m, 1 H), 1.81-1.91 (m, 1 H), 1.01 (d, 3 H). EI-LCMS(rel abundance), m/z 509.4 (MH^+, 94%); HPLC RT 3.19 min.

[459] Using methods described for Examples 138-141 above, other compounds were prepared using the appropriate starting materials, and are summarized below as Examples 142 and 143.

[460] **Example 142**

Preparation of ((1*S*)-5-{2-[1,4-dimethyl-2-(4-methylphenyl)-1*H*-imidazol-5-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid

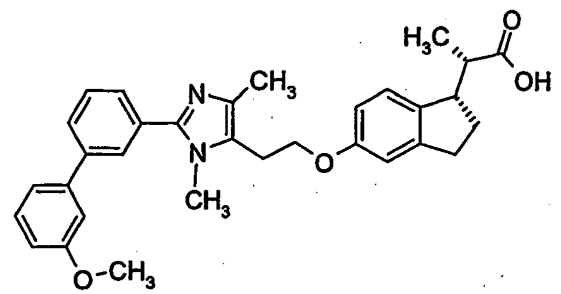


[461] ^{1}H NMR (300 MHz/ CD_3OD) δ 7.55 (d, 2 H), 7.48 (d, 2 H), 7.08 (d, 1 H), 6.77 (s, 1 H), 6.69 (d, 1 H), 4.22 (t, 2 H), 3.84 (s, 3 H), 3.43 (qr, 1 H), 3.24 (t, 2 H), 2.74-2.88 (m, 2

H), 2.66 (dd, 1 H), 2.47 (s, 3 H), 2.39 (s, 3 H), 2.26-2.37 (m, 2 H), 1.65-1.79 (m, 1 H). EI-LCMS(rel abundance), m/z 405.4 (MH+, 100%); HPLC RT 2.7 min.

[462] **Example 143**

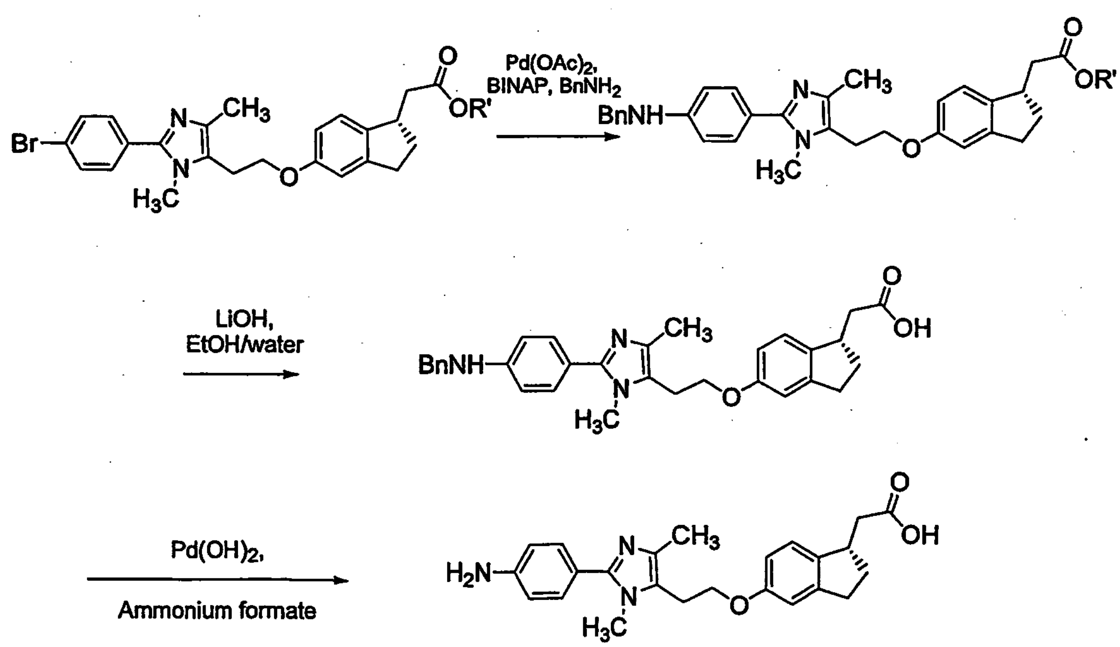
Preparation of (2*S*)-2-((1*S*)-5-{2-[2-(3'-methoxy-1,1'-biphenyl-3-yl)-1,4-dimethyl-1*H*-imidazol-5-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)propanoic acid



[463] ^{1}H NMR (CD_2Cl_2) δ 1.1 (d, 3H), 1.9 (m, 1H), 2.2 (m,1H), 2.4 (s, 3H), 2.8 (m, 3H), 3.2 (t, 2H), 3.5 (m, 1H), 3.9 (s, 6H), 4.2 (t, 2H), 6.6 (m, 1H), 6.8 (m, 1H), 7.0 (m, 1H) 7.1 (d, 1H), 7.2 (m, 2H), 7.4 (m, 1H), 7.6 (m, 1H), 7.7 (m, 1H), 7.8 (s, 1H), 7.9 (m, 1H); MS (ES) 511 $(MH)^+$; HPLC RT 3.03 min.

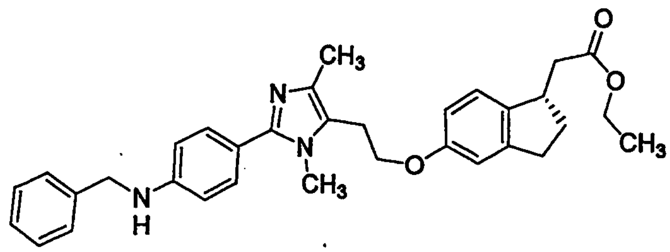
[464] Using the appropriate starting materials, Examples 144-146 were prepared by the methods exemplified by Reaction Scheme 19.

[465] **Reaction Scheme 19**



[466] **Example 144**

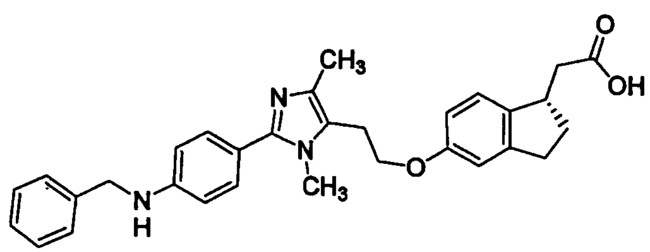
Preparation of ethyl [(1S)-5-(2-{2-[4-(benzylamino)-1,4-dimethyl-1H-imidazol-5-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl]acetate



[467] A dried flask was charged with palladium acetate (1 mg), BINAP (2.61 mg), and cesium carbonate (36.4mg, 0.11 mmol) and the mixture was degased. To this mixture was added a solution of ethyl ((1S)-5-{2-[2-(4-bromophenyl)-1,4-dimethyl-1H-imidazol-5-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)acetate (Example 138, 27.8 mg, 0.06 mmol) and benzyl amine (12.0 mg, 0.11 mmol) in toluene (1 mL). The reaction mixture was stirred at 85°C for 16 h. The crude product was cooled to rt, diluted with ethyl acetate, and then filtered through a Celite® plug. The solvent was then concentrated under reduced pressure and purified by Gilson HPLC system with 30% to 100% acetonitrile in water to provide 14 mg (48% yield) of desired product.

[468] **Example 145**

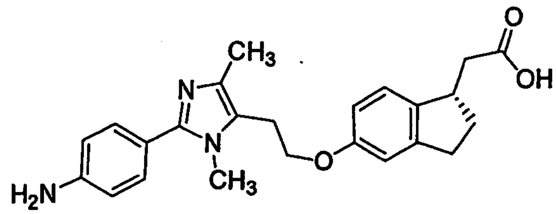
Preparation of [(1S)-5-(2-{2-[4-(benzylamino)-1,4-dimethyl-1H-imidazol-5-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl]acetic acid



[469] The compound was prepared via hydrolysis of Example 144 using the procedure described above for Example 141. ^1H NMR (300 MHz/ CD_3OD) δ 7.21-7.37 (m, 7 H), 7.07 (d, 1 H), 6.75-6.79 (m, 3 H), 6.67 (d, 1 H), 4.41 (s, 2 H), 4.19 (t, 2 H), 3.79 (s, 3 H), 3.31 (qr, 1 H), 3.20 (t, 2 H), 2.61-2.82 (m, 3 H), 2.21-2.41 (m, 5 H), 1.61-1.79 (m 1 H). ES-LCMS(rel abundance), RT= 2.98, m/z 496.4 (MH+, 100%).

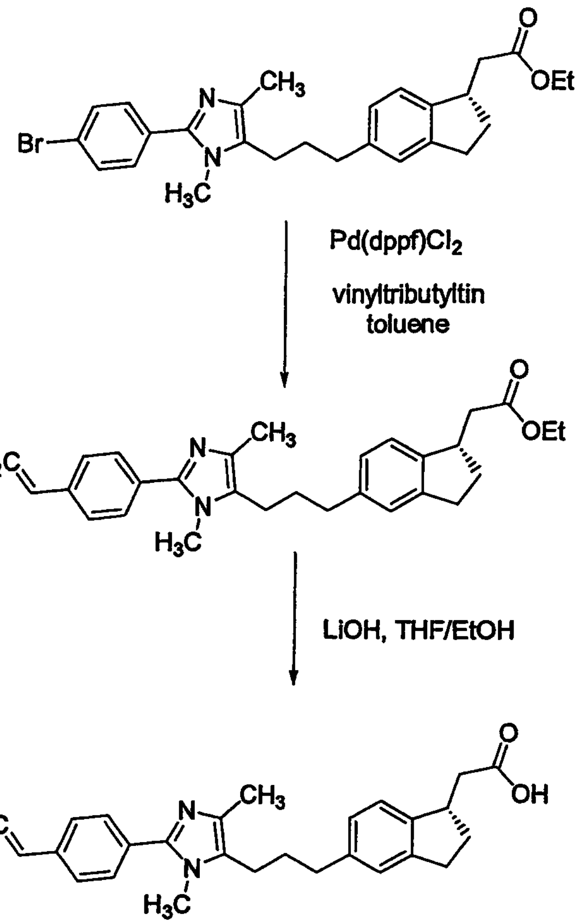
[470] **Example 146**

Preparation of [(1S)-5-(2-{2-[4-amino-1,4-dimethyl-1H-imidazol-5-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl]acetic acid



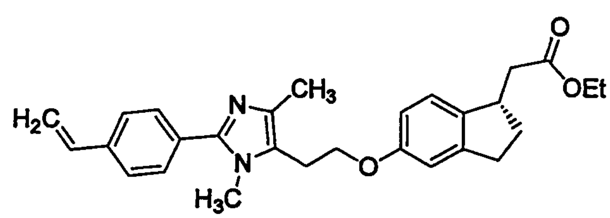
[471] [(1S)-5-(2-{2-[4-(benzylamino)-1,4-dimethyl-1H-imidazol-5-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl]acetic acid (Example 145, 7 mg, 0.014 mmol) was dissolved in methanol and ethyl acetate mixture (1/1), and added to $Pd(OH)_2$ (5 mg, 20% wt. on carbon, wet) in methanol (1 mL). NH_4HCO_2 (8.9 mg, 0.14 mmol) was added under nitrogen and the mixture was then heated to reflux. After 2 h, TLC showed the completion of the reaction and the crude product was cooled to rt, filtered through a Celite® plug, and concentrated under reduced pressure to afford an oil. The crude product was then purified by HPLC with 20% to 90% acetonitrile in water to provide 0.6 mg (10% yield) of desired product. ^{1}H NMR (300 MHz/ CD_3OD) δ 7.34 (d, 2 H), 7.08 (d, 1 H), 6.81 (d, 2 H), 6.76 (s, 1 H), 6.67 (d, 1 H), 4.32 (t, 2 H), 3.81 (s, 3 H), 3.44 (qr, 1 H), 3.23 (t, 2 H), 2.66-2.83 (m, 3 H), 2.29-2.42 (m, 5 H), 1.48-1.75 (m, 1 H). ES-LCMS(rel abundance), RT= 2.55, m/z 406.4 (MH+, 100%).

[472] **Reaction Scheme 20**



[473] **Example 147**

Preparation of ethyl [(1S)-5-(2-{2-[4-vinylphenyl-1,4-dimethyl-1H-imidazol-5-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl]acetate

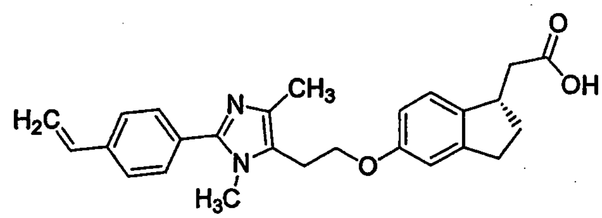


[474] To a mixture of vinyltributyltin (Aldrich, 178.0 mg, 0.56 mmol), ethyl ((1S)-5-{2-[2-(4-bromophenyl)-1,4-dimethyl-1H-imidazol-5-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)acetate (140 mg, 0.28 mmol), and [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (11.5 mg, 0.01 mmol) was added toluene (1 mL). The resulting solution was degassed with argon for 30 minutes, and then stirred at 110°C for 16 h. The reaction mixture was cooled to rt and diluted with 10 mL ethyl acetate. The organic layer was filtered through a silica plug and the filtrate concentrated under reduced

pressure. The crude product was then redissolved in methanol and filtered through a silica-octyl plug before preparative HPLC purification using 20 to 90% acetonitrile in water (0.1% TFA) gradient to afford 52 mg (41.6%) of the desired product. ^{1}H NMR (CD_2Cl_2) δ 7.48 (q, 4 H), 7.0 (d, 1 H), 6.52-6.72 (m, 3 H), 5.78 (d, 1 H), 5.29 (d, 1 H), 3.98-4.12 (m, 4 H), 3.59 (s, 3 H), 3.43 (qr, 1 H), 3.02 (2, H), 2.63-2.99 (m, 3 H), 2.29-2.51 (m, 2 H), 2.17 (s, 3 H), 1.61-1.73 (m, 1 H), 1.19 (t, 3 H).

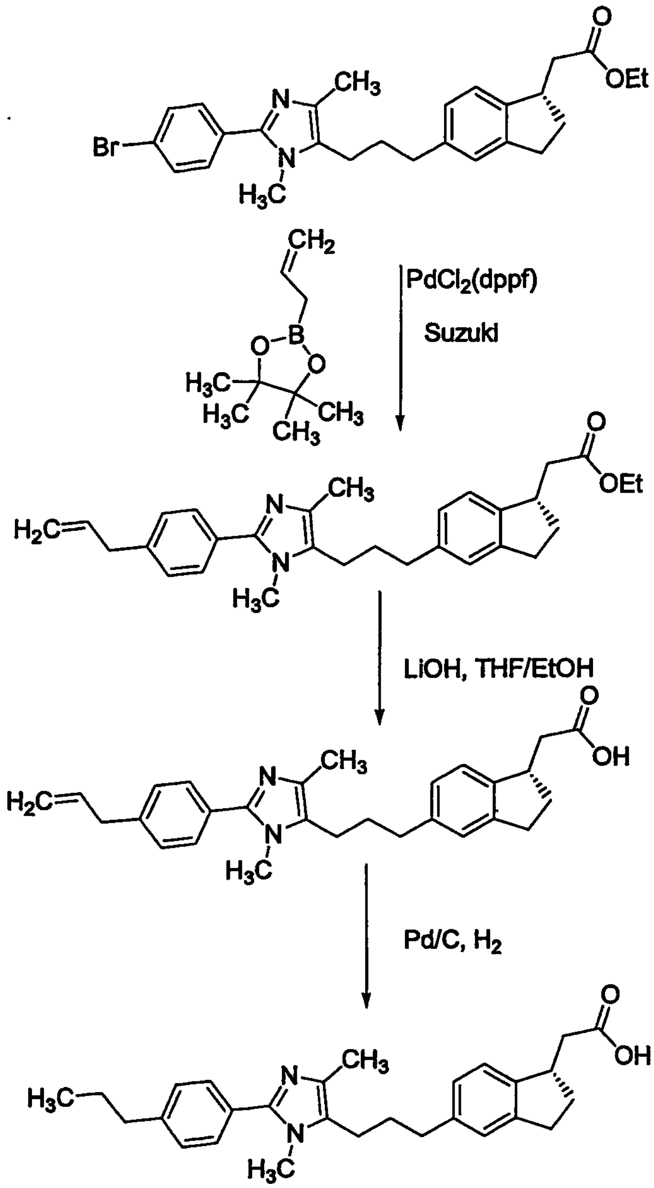
[475] **Example 148**

Preparation of [(1S)-5-(2-{2-[4-vinylphenyl-1,4-dimethyl-1H-imidazol-5-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl]acetic acid



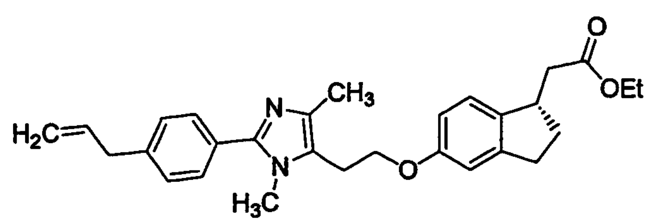
[476] This compound was prepared via hydrolysis procedure described in Example 141. ^{1}H NMR (CD_2Cl_2) δ 7.57 (q, 4 H), 7.0 (d, 1H), 6.75 (dd, 2 H), 6.55 (s, 1 H), 5.84 (d, 1 H), 5.36 (d, 1 H), 4.09 (t, 2 H), 3.73 (s, 3 H), 3.39 (qr, 1 H), 3.06 (t, 2 H), 2.53-2.82 (m, 3 H), 2.18-2.42 (m, 5 H), 1.59-1.75 (m, 1 H). ES-LCMS(rel abundance), RT= 2.78, m/z 417.4 (MH+, 100%).

[477] **Reaction Scheme 21**



[478] **Example 149**

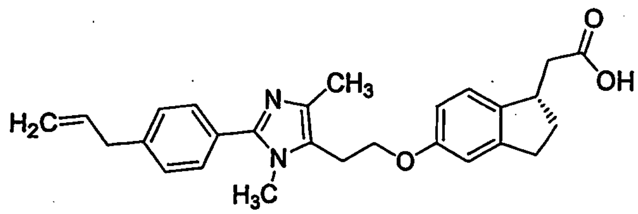
Preparation of ethyl [(1S)-5-(2-{2-[4-allylphenyl-1,4-dimethyl-1H-imidazol-5-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl]acetate



[479] This compound was prepared through a Suzuki coupling as described in Example 140.

[480] **Example 150**

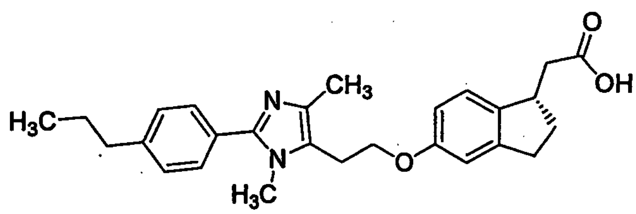
Preparation of [(1S)-5-(2-{2-[4-allylphenyl-1,4-dimethyl-1H-imidazol-5-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl]acetic acid



[481] This compound was prepared via the hydrolysis procedure described in Example 141. ^1H NMR (CD_2Cl_2) δ 7.49-7.68 (m, 4 H), 7.08 (d, 1 H), 6.78 (s, 1 H), 6.70 (d, 1 H), 6.52 (d, 1 H), 5.93-6.08 (m, 1 H), 5.08-5.18 (m 1 H), 4.22 (t, 2 H), 3.86 (s, 3 H), 3.38-3.55 (m, 1 H), 3.29 (t, 2 H), 2.62-2.91 (m, 3 H), 2.29-2.41 (m, 5 H), 1.91-1.96 (m, 2 H), 1.63-1.78 (m, 1 H). ES-LCMS(rel abundance), RT= 3.05, m/z 431.4 (MH+, 100%).

[482] **Example 151**

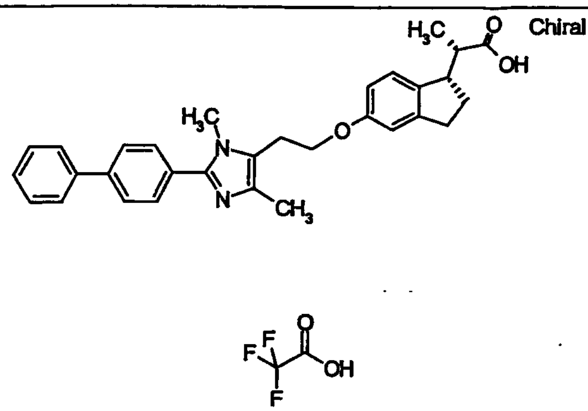
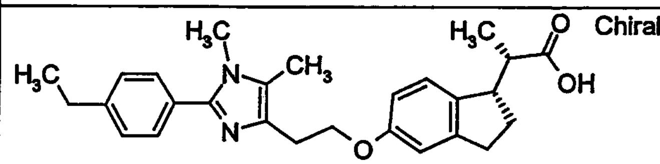
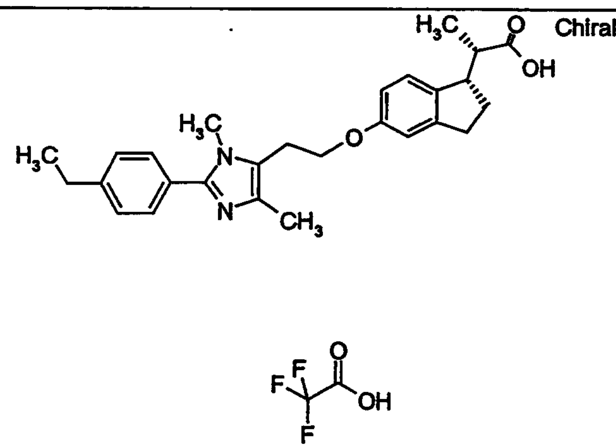
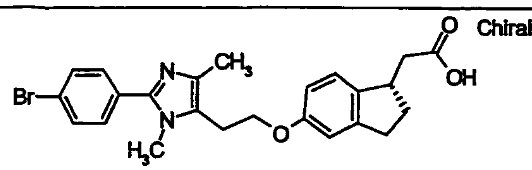
Preparation of [(1S)-5-(2-{2-[4-propylphenyl-1,4-dimethyl-1H-imidazol-5-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl]acetic acid

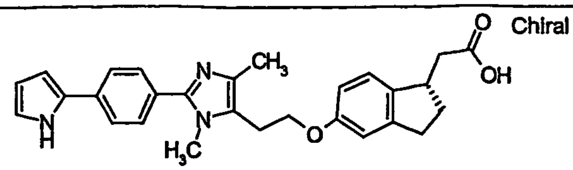
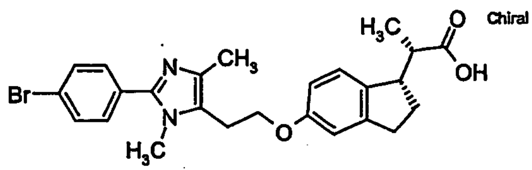
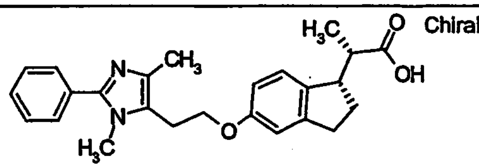
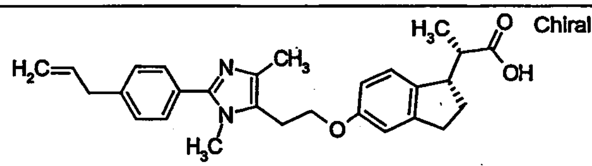
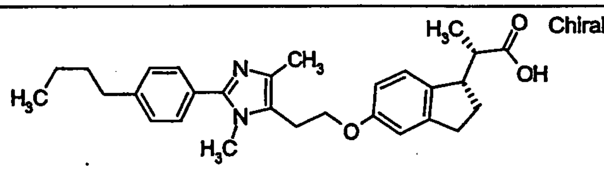
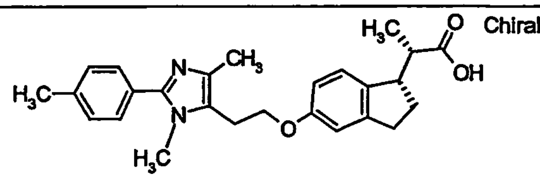
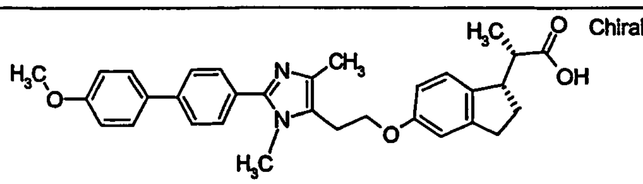
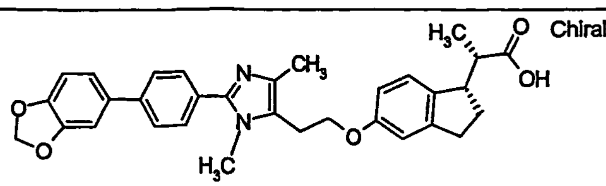


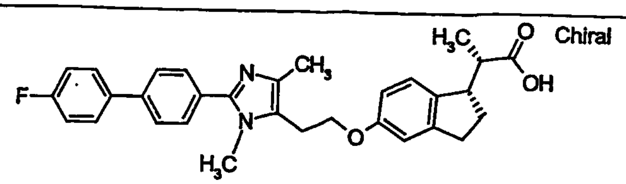
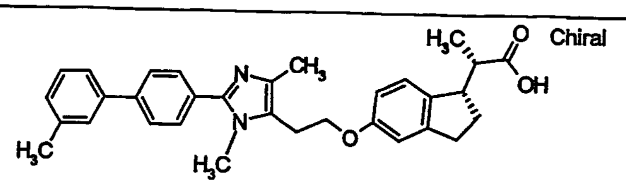
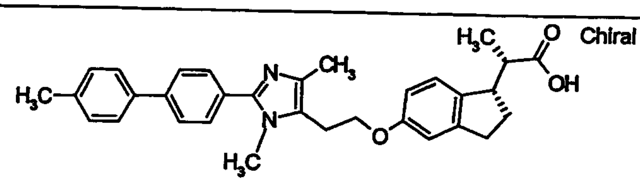
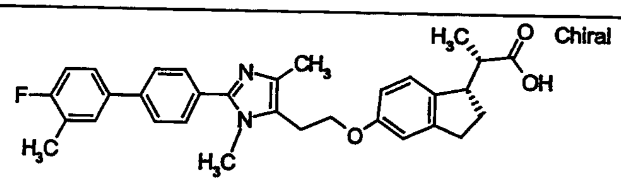
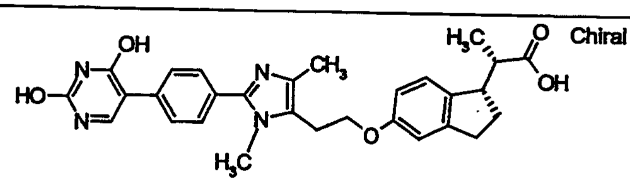
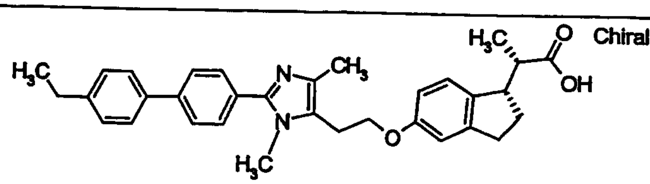
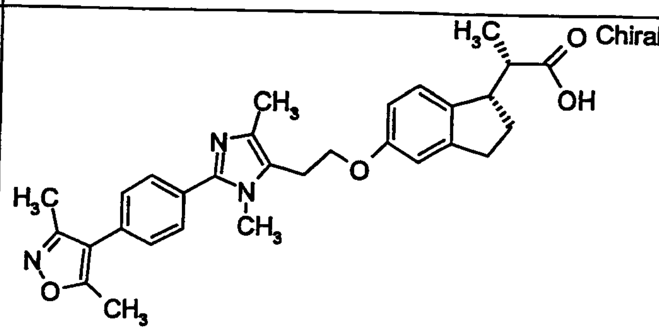
[483] To a 25 mL dried flask was added Pd/C (10% wt, 3 mg), and the flask was flushed with argon. Ethanol (0.5 mL) was added to the reaction vessel, followed by a solution of [(1S)-5-(2-{2-[4-allylphenyl-1,4-dimethyl-1H-imidazol-5-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl]acetic acid (1.6 mg, 0.04 mmol) in a mixture of ethyl acetate and ethanol (1/1). The flask was then flushed with hydrogen for 5 minutes and the mixture was then stirred under 1 atm of hydrogen for 16 h. The flask was flushed with argon and the reaction mixture was filtered through a Celite® plug. The filtrate was then concentrated under reduced pressure to afford 1.1 mg (68%) of desired product. ^1H NMR (CD_2Cl_2) δ 7.55 (q, 4 H), 7.07 (d, 1 H), 6.76 (s, 1 H), 6.68 (d, 1 H), 4.21 (t, 2 H), 3.84 (s, 3 H), 3.42 (qr, 1 H), 3.24 (t, 2 H), 2.61-2.92 (m 5 H), 2.26-2.40 (m, 5 H), 1.62-1.76 (m, 3 H), 0.96 (t, 3 H). ES-LCMS(rel abundance), RT= 3.13, m/z 433.4 (MH+, 100%).

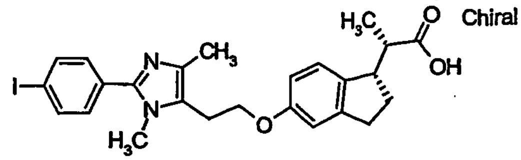
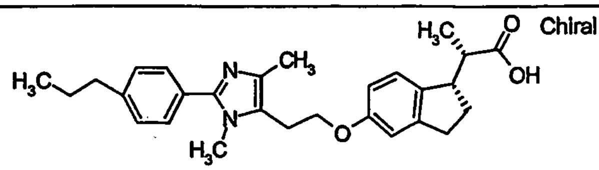
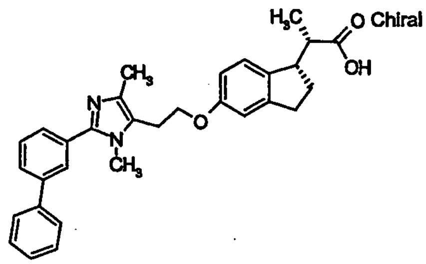
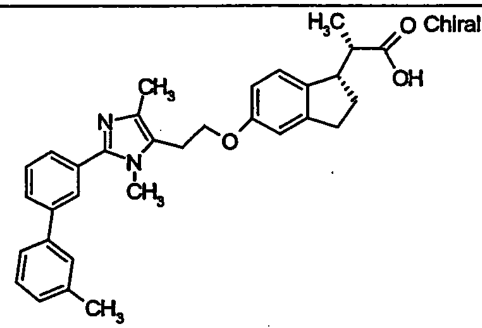
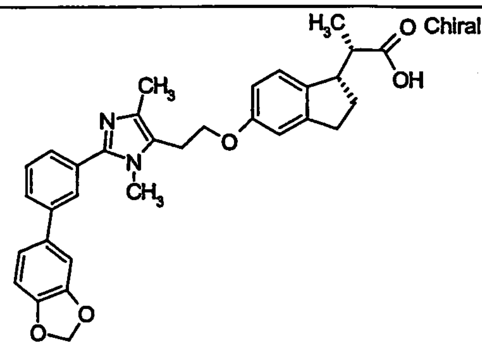
[484] Using the methods described above for Examples 108-151 the compounds of Table 11 were similarly prepared.

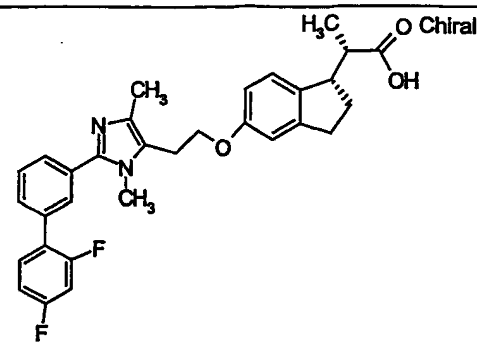
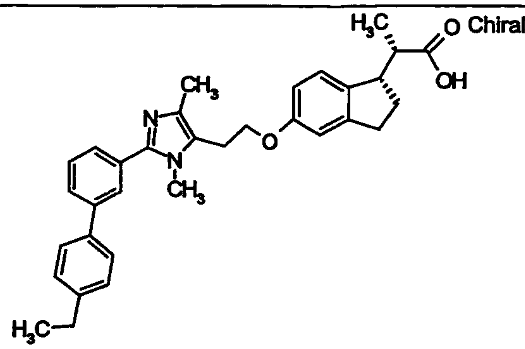
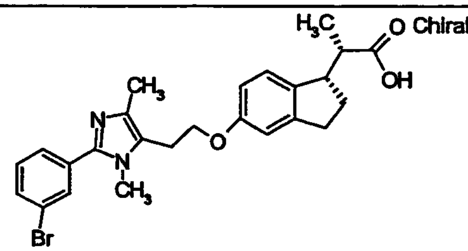
[485] **Table 11**

Example No.	Structure	HPLC RT (min)	EI-MS [M+H]+
152		3.27	481.4
153		3.12	433.4
154		3.13	433.4
155		2.98	469.3

Example No.	Structure	HPLC RT (min)	EI-MS [M+H]+
156		2.8	456.4
157		2.9	483.3
158		2.76	405.4
159		3.03	445.4
160		3.23	461.4
161		2.87	419.4
162		3.14	511.4
163		3.1	525.4

Example No.	Structure	HPLC RT (min)	EI-MS [M+H]+
164		3.15	499.4
165		3.24	495.4
166		3.21	495.4
167		3.23	513.4
168		2.61	515.4
169		3.3	509.4
170		2.85	505.4

Example No.	Structure	HPLC RT (min)	EI-MS [M+H]+
171		2.9	531.3
172		3.02	447.4
173		3.02	481
174		3.11	495
175		3.01	525

Example No.	Structure	HPLC RT (min)	EI-MS [M+H]+
176		3.06	517
177		3.21	509
178		2.83	485

[486] **Table 12**

Example No.	IUPAC Name
152	(2S)-2-((1S)-5-{2-[2-(1,1'-Biphenyl-4-yl)-1,4-dimethyl-1H-imidazol-5-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)propanoic acid trifluoroacetate
153	(2S)-2-((1S)-5-{2-[2-(4-Ethylphenyl)-1,5-dimethyl-1H-imidazol-4-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)propanoic acid trifluoroacetate
154	(2S)-2-((1S)-5-{2-[2-(4-Ethylphenyl)-1,4-dimethyl-1H-imidazol-5-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)propanoic acid trifluoroacetate

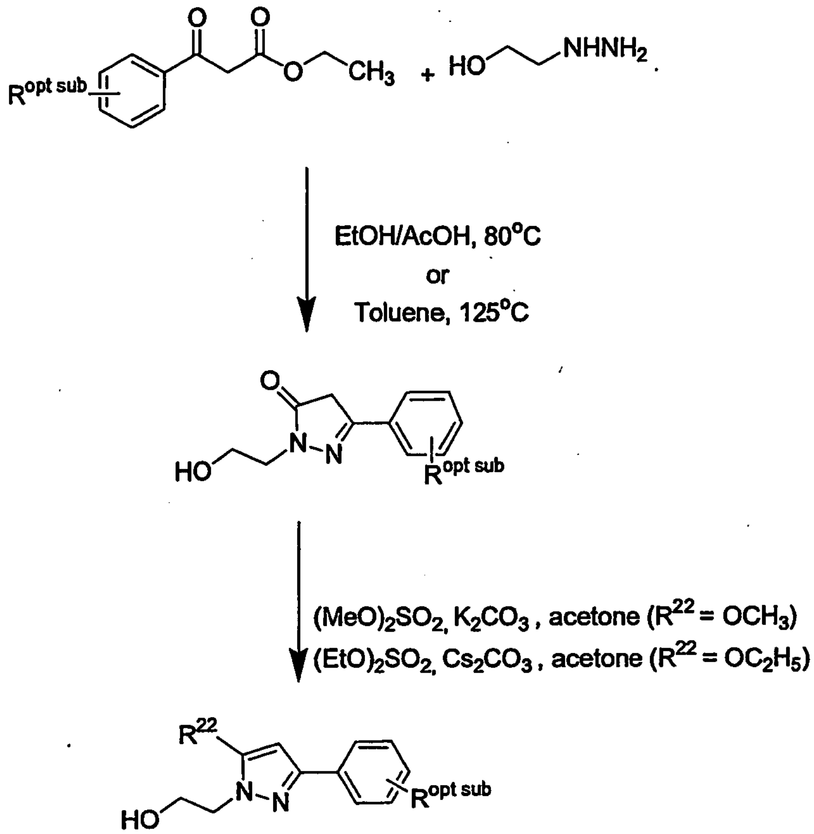
Example No.	IUPAC Name
155	((1S)-5-{2-[2-(4-Bromophenyl)-1,4-dimethyl-1H-imidazol-5-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)acetic acid
156	[(1S)-5-(2-{1,4-Dimethyl-2-[4-(1H-pyrrol-2-yl)phenyl]-1H-imidazol-5-yl}ethoxy)-2,3-dihydro-1H-inden-1-yl]acetic acid
157	(2S)-2-((1S)-5-{2-[2-(4-Bromophenyl)-1,4-dimethyl-1H-imidazol-5-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)propanoic acid
158	(2S)-2-{(1S)-5-[2-(1,4-Dimethyl-2-phenyl-1H-imidazol-5-yl)ethoxy]-2,3-dihydro-1H-inden-1-yl}propanoic acid
159	(2S)-2-((1S)-5-{2-[2-(4-Allylphenyl)-1,4-dimethyl-1H-imidazol-5-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)propanoic acid
160	(2S)-2-((1S)-5-{2-[2-(4-Butylphenyl)-1,4-dimethyl-1H-imidazol-5-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)propanoic acid
161	(2S)-2-((1S)-5-{2-[1,4-Dimethyl-2-(4-methylphenyl)-1H-imidazol-5-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)propanoic acid
162	(2S)-2-((1S)-5-{2-[2-(4'-Methoxy-1,1'-biphenyl-4-yl)-1,4-dimethyl-1H-imidazol-5-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)propanoic acid
163	(2S)-2-[(1S)-5-(2-{2-[4-(1,3-Benzodioxol-5-yl)phenyl]-1,4-dimethyl-1H-imidazol-5-yl}ethoxy)-2,3-dihydro-1H-inden-1-yl]propanoic acid
164	(2S)-2-((1S)-5-{2-[2-(4'-Fluoro-1,1'-biphenyl-4-yl)-1,4-dimethyl-1H-imidazol-5-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)propanoic acid
165	(2S)-2-((1S)-5-{2-[1,4-Dimethyl-2-(3'-methyl-1,1'-biphenyl-4-yl)-1H-imidazol-5-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)propanoic acid
166	(2S)-2-((1S)-5-{2-[1,4-Dimethyl-2-(4'-methyl-1,1'-biphenyl-4-yl)-1H-imidazol-5-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)propanoic acid
167	(2S)-2-((1S)-5-{2-[2-(4'-Fluoro-3'-methyl-1,1'-biphenyl-4-yl)-1,4-dimethyl-1H-imidazol-5-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)propanoic acid
168	(2S)-2-[(1S)-5-(2-{2-[4-(2,4-Dihydroxy-5-pyrimidinyl)phenyl]-1,4-dimethyl-1H-imidazol-5-yl}ethoxy)-2,3-dihydro-1H-inden-1-yl]propanoic acid
169	(2S)-2-((1S)-5-{2-[2-(4'-Ethyl-1,1'-biphenyl-4-yl)-1,4-dimethyl-1H-imidazol-5-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)propanoic acid
170	(2S)-2-[(1S)-5-(2-{2-[4-(3,5-Dimethyl-4-isoxazolyl)phenyl]-1,4-dimethyl-1H-imidazol-5-yl}ethoxy)-2,3-dihydro-1H-inden-1-yl]propanoic acid

Example No.	IUPAC Name
171	(2S)-2-((1S)-5-{2-[2-(4-Iodophenyl)-1,4-dimethyl-1H-imidazol-5-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)propanoic acid
172	(2S)-2-((1S)-5-{2-[1,4-Dimethyl-2-(4-propylphenyl)-1H-imidazol-5-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)propanoic acid
173	(2S)-2-((1S)-5-{2-[2-(1,1'-Biphenyl-3-yl)-1,4-dimethyl-1H-imidazol-5-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)propanoic acid
174	(2S)-2-((1S)-5-{2-[1,4-Dimethyl-2-(3'-methyl-1,1'-biphenyl-3-yl)-1H-imidazol-5-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)propanoic acid
175	(2S)-2-[(1S)-5-(2-{2-[3-(1,3-Benzodioxol-5-yl)phenyl]-1,4-dimethyl-1H-imidazol-5-yl}ethoxy)-2,3-dihydro-1H-inden-1-yl]propanoic acid
176	(2S)-2-((1S)-5-{2-[2-(2',4'-Difluoro-1,1'-biphenyl-3-yl)-1,4-dimethyl-1H-imidazol-5-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)propanoic acid
177	(2S)-2-((1S)-5-{2-[2-(4'-Ethyl-1,1'-biphenyl-3-yl)-1,4-dimethyl-1H-imidazol-5-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)propanoic acid
178	(2S)-2-((1S)-5-{2-[2-(3-Bromophenyl)-1,4-dimethyl-1H-imidazol-5-yl]ethoxy}-2,3-dihydro-1H-inden-1-yl)propanoic acid

[487] Reaction Schemes 22-26 summarize the synthetic methods utilized for the preparation of compounds of Formula (Ic). These methods were used to prepare Intermediates N, O, P, and Q and Examples 179-210 as specifically described below.

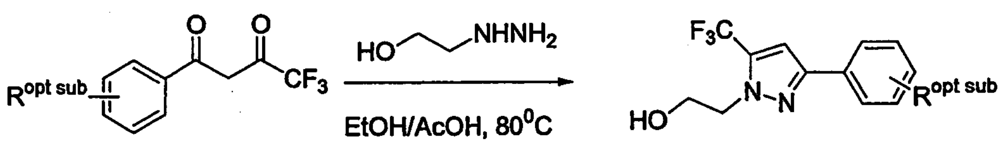
[488] **Preparation of Pyrazoles**

Reaction Scheme 22

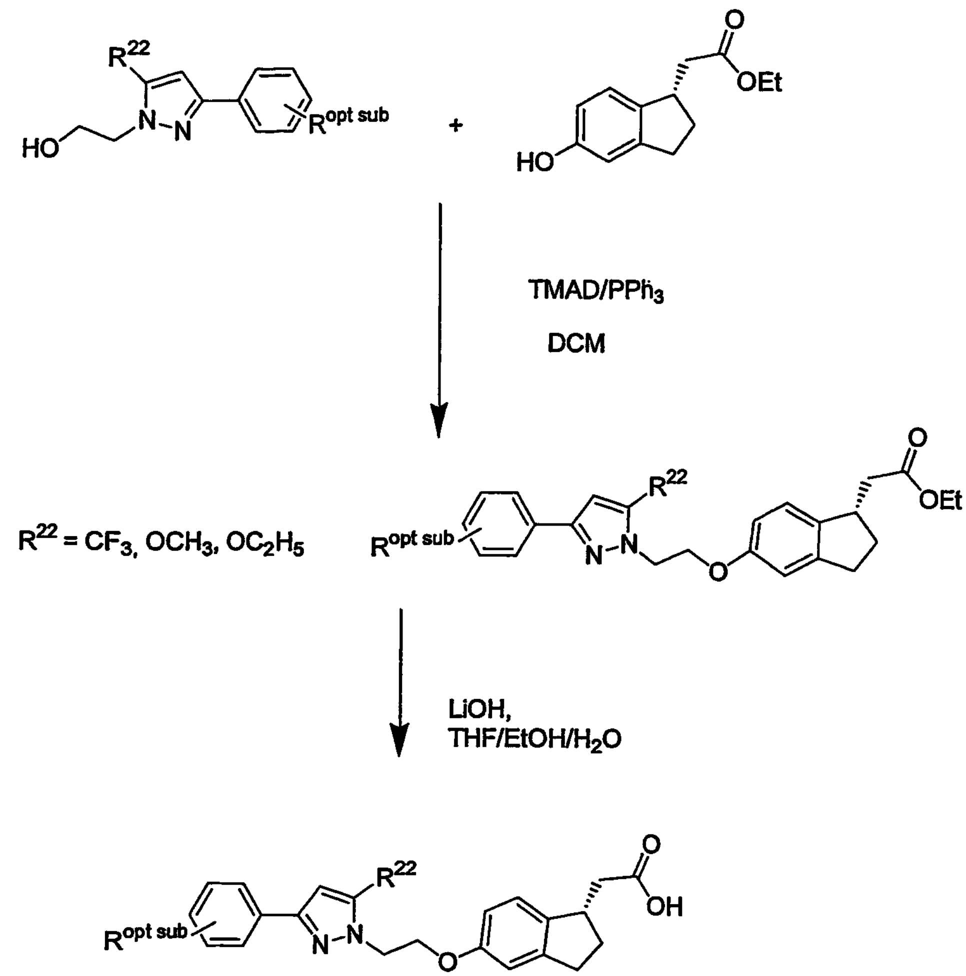


[489] **Reaction Scheme 23**

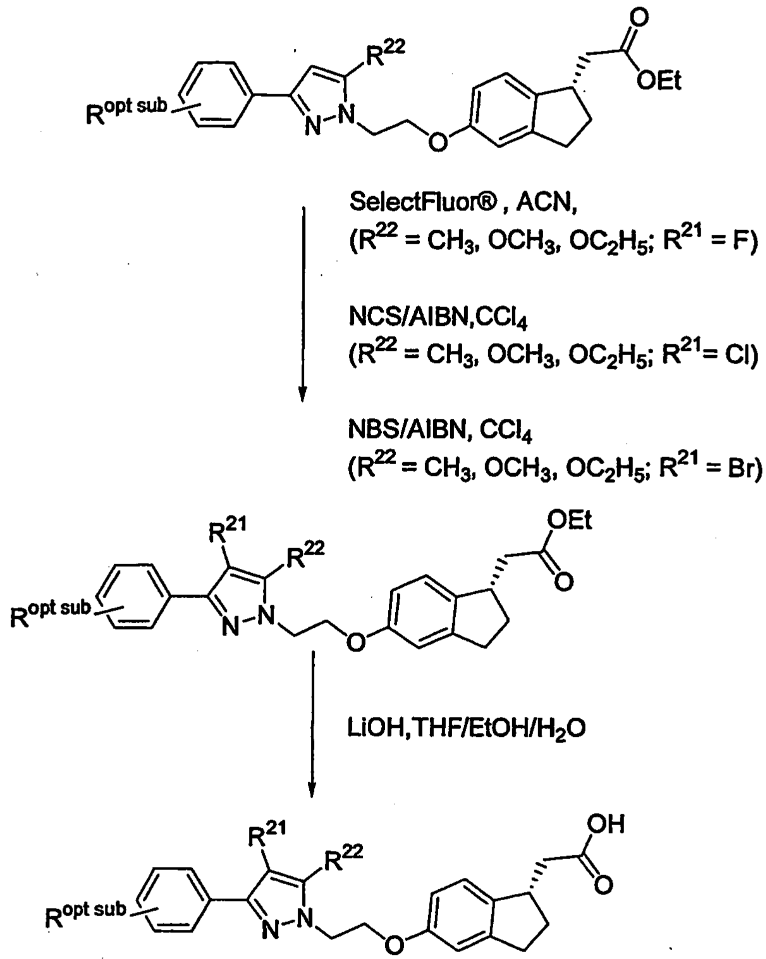
(when $R^{22} = CF_3$)



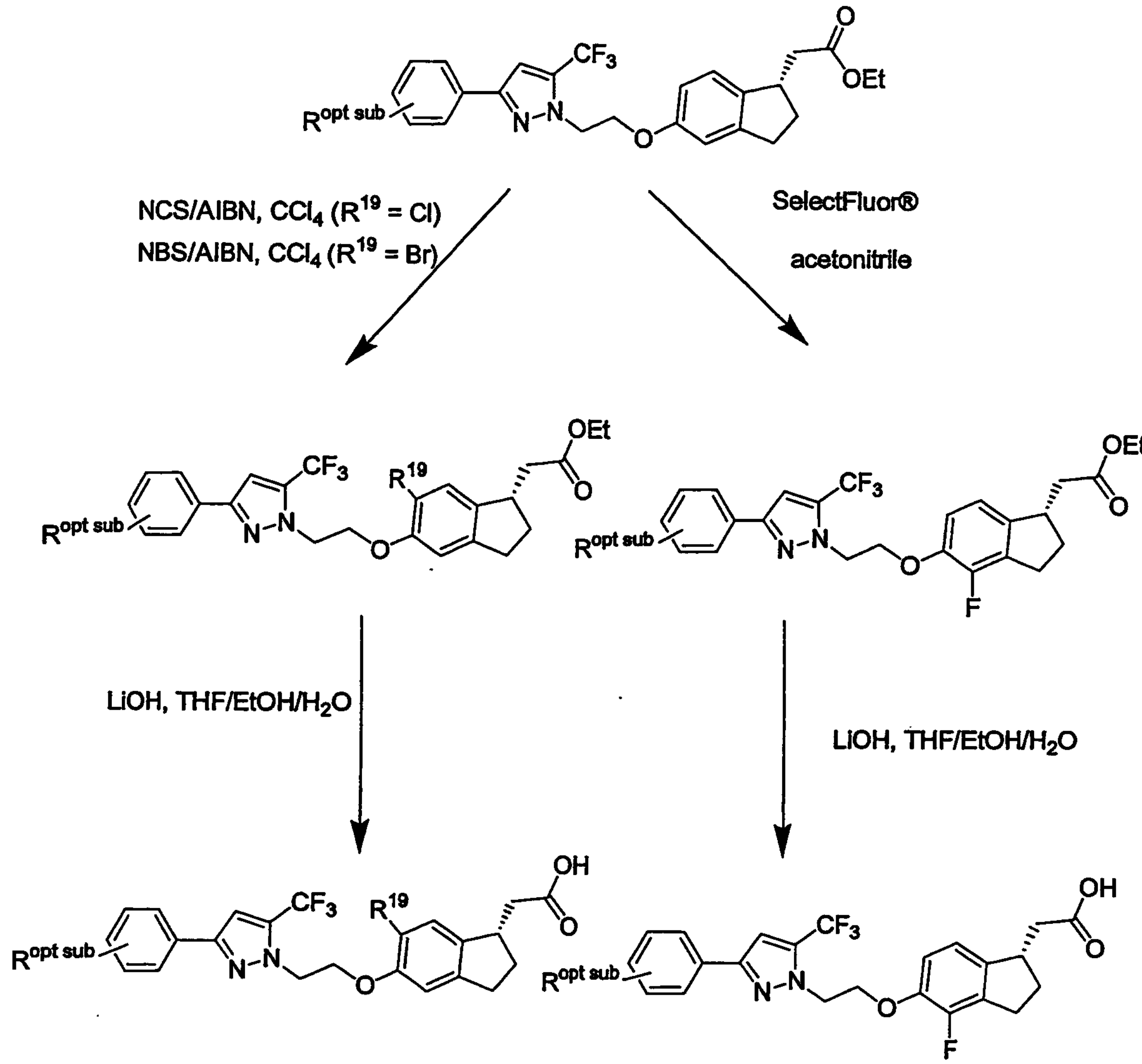
[490] **Reaction Scheme 24**



[491] <u>**Reaction Scheme 25**</u>

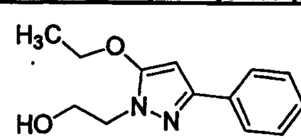


[492] **Reaction Scheme 26**

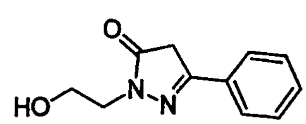


[493] **Intermediate N**

Preparation of 2-(5-ethoxy-3-phenyl-1*H*-pyrazol-1-yl)ethanol



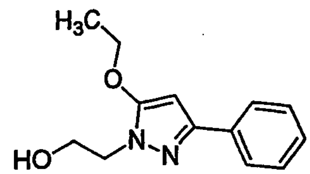
[494] Step 1. Preparation of 2-(2-hydroxyethyl)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one



[495] A mixture of ethyl benzoylacetate (50 mL, 0.26 mol) and 2-hydoxyethylhydrazine (20 mL, 0.29 mol) in 400 mL toluene was heated overnight at 125°C (oil bath) with an attached Dean Stark tube. The mixture was cooled down to rt, filtered, and treated with

ether to form 41 g of desired product as a light brown precipitate (0.2 mol, 77% yield). ^{1}H NMR (DMSO): δ 3.85 (t, 2H), 4.1 (t, 2H), 5.90 (s, 1H), 7.35 (t, 1H), 7.5 (m, 2H), 7.8 (d, 2H); HPLC/MS $(M+H)^+$ m/z 205.

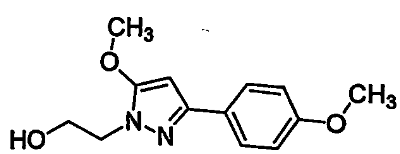
[496] Step 2. Preparation of 2-(5-ethoxy-3-phenyl-1*H*-pyrazol-1-yl)ethanol



[497] A mixture of 2-(2-hydroxyethyl)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (10 g, 0.049 mol), cesium carbonate (24 g, 0.073 mol), and diethyl sulfate (6.4 mL, 0.049 mol) in acetone (400 mL) was heated to reflux for 3 h. The solvent was filtered, and concentrated. The resulting residue was dissolved with CH_2Cl_2 and passed through a short column and eluted with CH_2Cl_2. After drying under vacuum at 40°C, 8.75 g of the desired product was isolated as a white precipitate (37.6 mmol, 77% yield). R_f = 0.47 (EtOAc-hexanes, 1:1); HPLC/MS $(M+H)^+$ m/z 233; ^{1}H NMR ($CDCl_3$): δ 1.45 (t, 3H), 4.0 (t, 2H), 4.1 (t, 2H), 4.2 (q, 2H), 5.85 (s, 1H), 7.30 (d, 1H), 7.35 (t, 2H), 7.75 (d, 2H).

[498] **Intermediate O**

Preparation of 2-[5-methoxy-3-(4-methoxy-phenyl)-1*H*-pyrazol-1-yl]ethanol



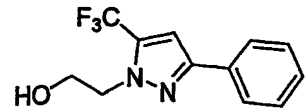
[499] Step 1. A mixture of ethyl 3-(4-methoxyphenyl)-3-oxo-propanoate (500 mg, 2.25 mmol), 2-hydroxyethylhydrazine (152 µL, 2.25 mmol), and glacial acetic acid (50 µL) in 5 mL EtOH was heated at 80°C (oil bath), monitoring for the disappearance of starting material. When the reaction was complete, the mixture was cooled down and the solvents were removed. The crude material, 2-(2-hydroxyethyl)-5-(4-methoxy-phenyl)-2,4-dihydro-3*H*-pyrazol-3-one, thus obtained was used in the next step without preparation.

[500] Step 2. A mixture of 2-(2-hydroxyethyl)-5-(4-methoxy-phenyl)-2,4-dihydro-3*H*-pyrazol-3-one (2.25 mmol), potassium carbonate (0.93 g, 6.75 mmol), and dimethyl sulfate (213 µL, 2.25 mmol) in acetone (10 mL) was stirred at ambient temperature for 3 h. The mixture was filtered, and concentrated. The resulting residue was purified using Biotage parallel purification system with 20%, 50%, and then 100% EtOAc/hexanes. The

desired product was obtained (151 mg, 0.61 mmol, 27%); HPLC/MS $(M+H)^+$ m/z 249; ^{1}H NMR ($CDCl_3$): δ 3.80 (s, 3H), 3.92 (s, 3H), 4.00 (t, 2H), 4.10 (t, 2H), 5.90 (s, 1H), 6.90 (d, 2H), 7.70 (d, 2H).

[501] **Intermediate P**

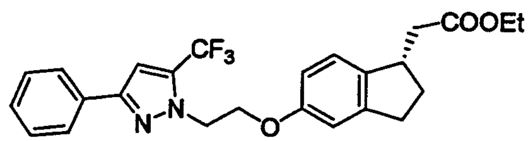
Preparation of 2-(5-trifluoromethyl-3-phenyl-1*H*-pyrazol-1-yl) ethanol



[502] A mixture of 4, 4, 4,-trifluoro-phenylbutane-1,3-dione (500 mg, 2.31 mmol), 2-hydoxyethylhydrazine (157 µL, 2.31 mmol), and glacial acetic acid (100 µL) in 5 mL EtOH was heated at 80°C (oil bath) for 15 h. The mixture was cooled down and the solvents were removed. The crude material was purified by flash chromatography and gave the title compound (381 mg, 64%); HPLC/MS $(M+H)^+$ m/z 257; ^{1}H NMR ($CDCl_3$): δ 2.96 (t, 1H), 4.05 (t, 2H), 4.14 (t, 2H), 6.60 (s, 1H), 7.48 (m, 5H).

[503] **Example 179**

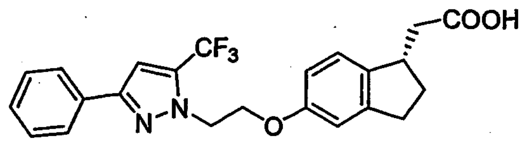
Preparation of ethyl ((1*S*)-5-{2-[3-phenyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetate



[504] A mixture of 2-(5-trifluoromethyl-3-phenyl-1*H*-pyrazol-1-yl) ethanol (128 mg, 0.5 mmol), ethyl (1*S*)-(5-hydroxy-2,3-dihydro-1*H*-inden-1-yl)acetate (110 mg, 0.5 mmol), TMAD (129.2 mg, 0.75 mmol), and Ph_3P (197 mg, 0.75 mmol) in CH_2Cl_2 (5.0 mL) was stirred under argon overnight. The solvent was removed. Flash chromatograph (silica gel) of the crude material using 30% EtOAc/hexanes gave the desired product (189 mg, 83%); HPLC/MS $(M+H)^+$ m/z 459; ^{1}H NMR ($CDCl_3$): δ 1.27 (t, 3H), 1.75 (m, 1H), 2.38 (m, 2H), 2.70 (dd, 1H), 2.85 (m, 2H), 3.50 (m, 1H), 4.20 (q, 2H), 4.40 (t, 2H), 4.50 (t, 2H), 6.55(s, 1H), 6.60 (d, 1H), 6.64 (br. s, 1H), 7.02 (d, 1H), 7.50 (m, 5H).

[505] **Example 180**

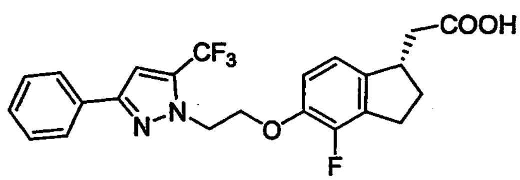
Preparation of ((1*S*)-5-{2-[3-phenyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid



[506] To a solution of ethyl ((1*S*)-5-{2-[3-phenyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetate (37.4 mg, 0.08 mmol) in THF/EtOH/H_2O (2:2:1, 1.0 mL) was added aqueous LiOH (2M, 160 μL). The resulting solution was stirred overnight at ambient temperature. The mixture was diluted with water and it was acidified to pH = 3 using aqueous HCl (1N). The compound was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and evaporated. Preparative TLC purification of the residue using 5% MeOH/CH_2Cl_2 gave the title compound (18 mg, 48%); HPLC/MS $(M+H)^+$ m/z 431; ^{1}H NMR ($CDCl_3$): δ 1.78 (m, 1H), 2.42 (m, 2H), 2.84 (m, 3H), 3.50 (m, 1H), 4.40 (t, 2H), 4.52 (t, 2H), 6.58 (s, 1H), 6.60 (d, 1H), 6.80 (s, 1H), 7.08 (d, 1H), 7.50 (m, 5H).

[507] **Example 181**

Preparation of ((1*S*)-4-fluoro-5-{2-[3-phenyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid

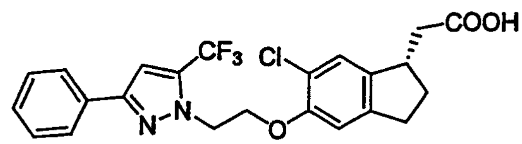


[508] A mixture of ethyl ((1*S*)-5-{2-[3-phenyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetate (Example 179, 40 mg, 0.09 mmol), SelectFluor® (35 mg, 0.11 mmol) in acetonitrile (2.0 mL) was stirred overnight at ambient temperature. After removal of solvent, preparative TLC purification of the residue using 20% EtOAc/hexanes gave ethyl 2-((1*S*)-4-fluoro-5-{2-[3-phenyl-5 (trifluoromethyl)pyrazolyl]ethoxy} indanyl)acetate, which was then dissolved in THF/EtOH/H_2O (2:2:1, 1.0 mL). The resulting solution was treated with aqueous LiOH (2M, 76 μL) overnight at ambient temperature. The mixture was diluted with water and the pH was adjusted to 3 using aqueous HCl (1N). The compound was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and evaporated. Preparative TLC purification of the residue using 5% MeOH/CH_2Cl_2 gave the title compound (2.4 mg, 6% over the two steps); HPLC/MS $(M+H)^+$ m/z 449; ^{1}H NMR ($CDCl_3$): δ 1.7 (m, 1H), 2.30

(m, 2H), 2.70 (m, 3H), 3.40 (m, 1H), 4.40 (t, 4H), 6.42 (s, 1H), 6.60 (d, 1H), 6.80 (d, 1H), 7.45 (m, 5H).

[509] **Example 182**

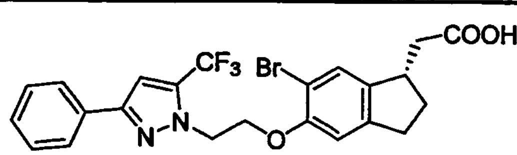
Preparation of ((1*S*)-6-chloro-5-{2-[3-phenyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid



[510] A mixture of ethyl ((1*S*)-5-{2-[3-phenyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetate (Example 179, 40 mg, 0.09 mmol), NCS (23 mg, 0.17 mmol), and a catalytic amount of AIBN in CCl_4 (2.0 mL) was stirred overnight at 60°C. After removal of solvent, preparative TLC purification of the residue using 20% EtOAc/hexanes gave ethyl 2-((1*S*)-6-chloro-5-{2-[3-phenyl-5-(trifluoromethyl)pyrazolyl] ethoxy}indanyl)acetate (10.5 mg, 24%), which was then dissolved in THF/EtOH/H_2O (2:2:1, 1.0 mL). The resulting solution was treated with aqueous LiOH (2M, 120 µL) overnight at ambient temperature. The mixture was diluted with water and the pH was adjusted to 3 using aqueous HCl (1N). The compound was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and evaporated. Preparative TLC purification of the residue using 5% MeOH/CH_2Cl_2 gave the title compound (3.8 mg, 38%); HPLC/MS $(M+H)^+$ m/z 465; ^1H NMR ($CDCl_3$): δ 1.68 (m, 1H), 2.35 (m, 2H), 2.78 (m, 3H), 3.42 (m, 1H), 4.43 (t, 4H), 6.43 (s, 1H), 6.62 (s, 1H), 7.08 (s, 1H), 7.45 (m, 5H).

[511] **Example 183**

Preparation of ((1*S*)-6-bromo-5-{2-[3-phenyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid

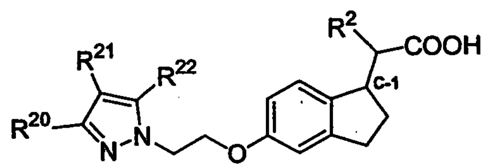


[512] A mixture of ethyl 2-((1*S*)-5-{2-[3-phenyl-5-(trifluoromethyl)pyrazolyl]ethoxy}indanyl) acetate (Example 179, 40 mg, 0.09 mmol), NBS (31 mg, 0.17 mmol), and catalytic amount of AIBN in CCl_4 (2.0 mL) was stirred overnight at 60°C. After removal of solvent, preparative TLC purification of the residue using 20% EtOAc/hexanes gave ethyl 2-((1*S*)-6-bromo-5-{2-[3-phenyl-5-(trifluoromethyl)pyrazolyl]ethoxy}indanyl)acetate (31.1 mg, 64%), which was then dissolved in THF/EtOH/H_2O (2:2:1, 1.0 mL). The resulting solution was treated with

aqueous LiOH (2M, 120 μL) overnight at ambient temperature. The mixture was diluted with water and the pH was adjusted to 3 using aqueous HCl (1N). The compound was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and evaporated. Preparative TLC purification of the residue using 5% MeOH/CH_2Cl_2 gave the desired product (10 mg, 34%); HPLC/MS $(M+H)^+$ m/z 510; ^{1}H NMR ($CDCl_3$): δ 1.70 (m, 1H), 2.35 (m, 2H), 2.75 (m, 3H), 3.42 (m, 1H), 4.44 (t, 4H), 6.45 (s, 1H), 6.64 (s, 1H), 7.10 (s, 1H), 7.40 (m, 3H), 7.50 (m, 2H).

[513] By using the methods described for Intermediates O-P and Examples 180-183 and by substituting the appropriate starting materials, compounds listed in Tables 13-15 below were similarly prepared.

[514] **Table 13**



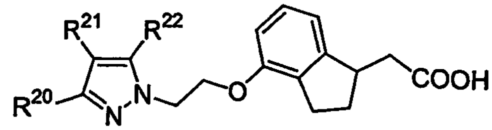
Example No.	R^{20}	R^{21}	R^{22}	R^2	LC/MS [M+H]+	C-1 stereo-isomer
184	Ph	H	EtO	H	407.5	*S*
185	4-COOH-Ph	H	EtO	H	451.5	*S*
186	Ph	F	Me	H	395.4	*S*
187	Ph	Cl	Me	H	411.4	*S*
188	Ph	Br	Me	H	456.3	*S*
189	4-MeO-Ph	H	MeO	H	423.4	*S*
190	4-CF_3-Ph	H	MeO	H	461.4	*S*
191	4-MeO-Ph	F	MeO	H	441.4	*S*
192	4-CF_3-Ph	F	MeO	H	479.4	*S*
193	4-CF_3-Ph	Br	MeO	H	540.4	*S*
194	Ph	H	Me	H	377.3	*S*

Example No.	R^{20}	R^{21}	R^{22}	R^2	LC/MS [M+H]+	C-1 stereo-isomer
195	Ph	H	Me	Et	405.4	*R* & *S*

[515] **Table 14**

Example No.	IUPAC Name
184	{(1*S*)-5-[2-(5-Ethoxy-3-phenyl-1*H*-pyrazol-1-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic acid
185	4-[1-(2-{[(1*S*)-1-(Carboxymethyl)-2,3-dihydro-1*H*-inden-5-yl]oxy}ethyl)-5-ethoxy-1*H*-pyrazol-3-yl]benzoic acid
186	{(1*S*)-5-[2-(4-Fluoro-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic acid
187	{(1*S*)-5-[2-(4-Chloro-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic acid
188	{(1*S*)-5-[2-(4-Bromo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic acid
189	((1*S*)-5-{2-[5-Methoxy-3-(4-methoxyphenyl)-1*H*-pyrazol-1-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid
190	[(1*S*)-5-(2-{5-Methoxy-3-[4-(trifluoromethyl)phenyl]-1*H*-pyrazol-1-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic acid
191	((1*S*)-5-{2-[4-Fluoro-5-methoxy-3-(4-methoxyphenyl)-1*H*-pyrazol-1-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid
192	[(1*S*)-5-(2-{4-Fluoro-5-methoxy-3-[4-(trifluoromethyl)phenyl]-1*H*-pyrazol-1-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic acid
193	[(1*S*)-5-(2-{4-Bromo-5-methoxy-3-[4-(trifluoromethyl)phenyl]-1*H*-pyrazol-1-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic acid
194	{(1*S*)-5-[2-(5-Methyl-3-phenyl-1*H*-pyrazol-1-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic acid
195	2-{5-[2-(5-Methyl-3-phenyl-pyrazol-1-yl)-ethoxy]-indan-1-yl}-butyric acid

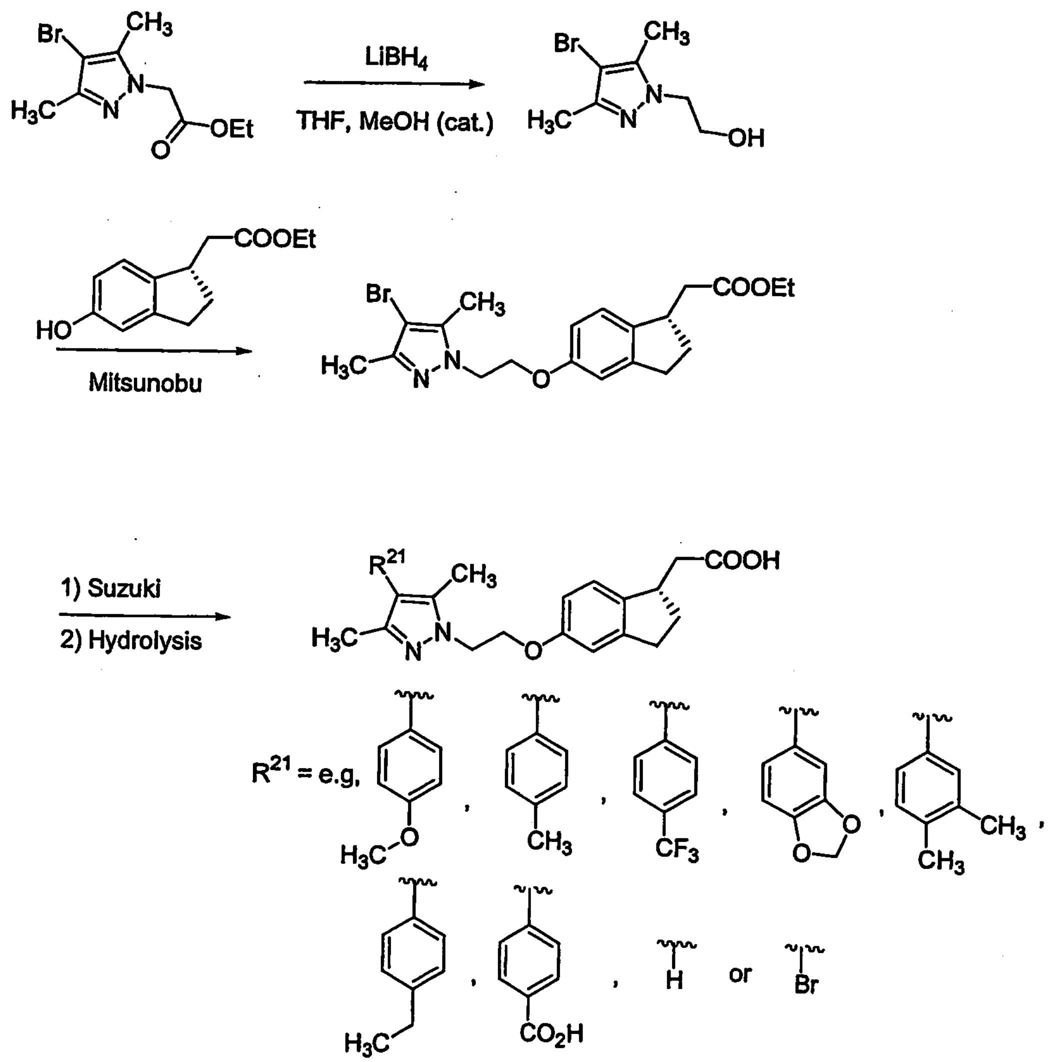
[516] **Table 15**



Example No.	R^{20}	R^{21}	R^{22}	LC-MS $[M+H]^+$
196	Ph	H	Me	377.2
IUPAC Name: {4-[2-(5-Methyl-3-phenyl-1*H*-pyrazol-1-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic acid				

[517] Reaction Scheme 27 summarizes the steps utilized for the preparation of Intermedaite Q and Examples 197-210.

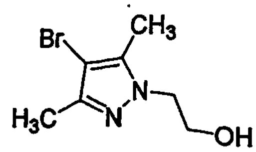
[518] **Reaction Scheme 27**



[519]

Intermediate Q

Preparation of 2-(4-bromo-3,5-dimethyl-1*H*-pyrazol-1-yl)ethanol

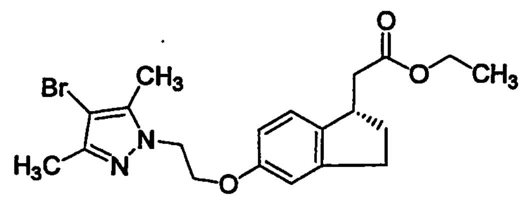


[520] The pyrazole ester (commercially available, 2 g, 7.69 mmol) was dissolved in THF (20 mL) and methanol (0.5 mL), and solid $LiBH_4$ (248 mg, 11.39 mmol) was added in 50 mg quantities at rt. The reaction was complete within an hour after addition. The solvent was reduced to half volume and then poured into ice water (30 mL). The mixture was then acidified by slowly adding 1N HCl until pH reached 6. Purification by flash chromatography with 80% ethyl acetate in hexanes afforded 1.2 g of white solid product. ^{1}H NMR ($CDCl_3$-d_1): δ 4.08 (t, 2 H), 3.96 (t, 2 H), 2.24 (s, 3 H), 2.19 (s, 3 H).

[522]

Example 197

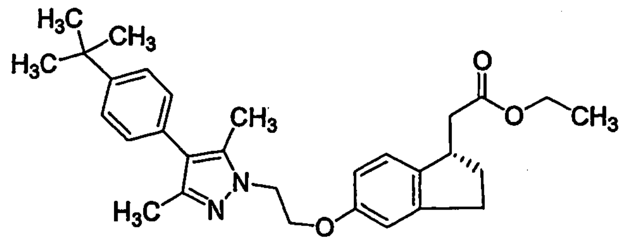
Preparation of ethyl {(1*S*)-5-[2-(4-bromo-3,5-dimethyl-1*H*-pyrazol-1-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate



Ethyl (5-hydroxy-2,3-dihydro-1*H*-inden-1-yl)acetate (Intermediate D, 620 mg, 2.83 mmol), pyrazole alcohol (Intermediate Q, 700 mg, 2.95 mmol), ADDP (1.12 g, 4.43 mmol), and Ph_3P (1.16 g, 4.43 mmol) in 15 mL anhydrous THF was stirred at rt under argon for 3 days. The mixture was treated with 5 mL hexanes and the solid was removed by filtration. THF was removed under reduced pressure. The crude product was purified by flash chromatography with 10% ethyl acetate in hexanes to afford 0.83 g (1.61 mmol, 68%) of the title compound. ^{1}H NMR ($CDCl_3$-d_1): δ 7.00 (d, 1 H), 6.58-6.69 (m, 2 H), 4.36 (t, 2 H), 4.21 (t, 2 H), 4.16 (q, 2 H), 3.42-3.38 (m, 1 H), 2.76-2.89 (m, 2 H), 2.65 (dd, 1 H), 2.32-2.42 (m, 2 H), 2.28 (s, 3 H), 2.18 (s, 3 H), 1.68-1.80 (m, 1 H), 1.22 (t, 3 H).

[523] **Example 198**

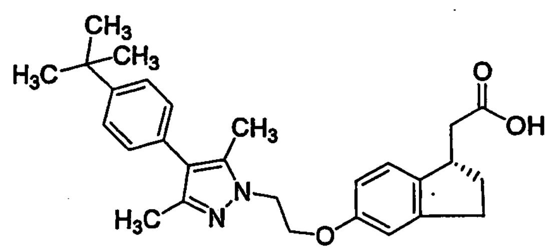
Preparation of ethyl ((1*S*)-5-{2-[4-(4-*tert*-butylphenyl)-3,5-dimethyl-1*H*-pyrazol-1-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetate



[524] To a mixture of 4-*tert*-butylphenylboronic acid (36 mg, 0.19 mmol), ethyl {(1*S*)-5-[2-(4-bromo-3,5-dimethyl-1*H*-pyrazol-1-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetate (40 mg, 0.1 mmol), and [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (8 mg, 0.01 mmol) was added toluene (0.8 mL) and dioxane (0.2 mL). The resulting solution was degassed under argon for 0.5 h, followed by addition of sodium bicarbonate solution (2 M, 0.2 mL), and then heated to 85°C for 48 h. The reaction mixture was allowed to cool to rt. The solvent was removed under reduced pressure and the crude product was subjected to the hydrolysis as described in Example 199 without purification.

[525] **Example 199**

Preparation of ((1*S*)-5-{2-[4-(4-*tert*-butylphenyl)-3,5-dimethyl-1*H*-pyrazol-1-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid



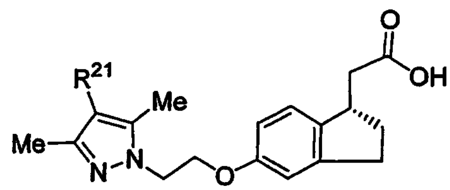
[526] To a solution of ethyl ((1*S*)-5-{2-[4-(4-*tert*-butylphenyl)-3,5-dimethyl-1*H*-pyrazol-1-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetate (crude product from Example 198) in an ethanol/water mixture (1/1) was added lithium hydroxide (42 mg, 1 mmol), and the mixture was heated to 40°C for 1.5 h. The reaction mixture was then allowed to cool to rt, the pH of the solution was adjusted to 5 with 0.5N HCl, extracted with ethyl acetate, and dried with Na_2SO_4. The solvent was removed under reduced pressure and the crude product was subjected to HPLC purification with gradient solution from 0% acetonitrile in water to 70% acetonitrile in water to afford 12.8 mg of the title compound. ^1H NMR ($CDCl_3$): δ 7.46 (d, 2 H), 7.16 (d, 2 H), 7.08 (d, 1 H), 6.60-6.73 (m, 2 H), 4.78 (t, 2 H), 4.39

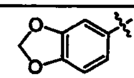
(t, 2 H), 3.42-3.60 (m, 1 H), 2.70-2.98 (m, 3 H), 2.38-2.45 (m, 2 H), 2.42 (s, 3 H), 2.37 (s, 3 H), 1.70-1.84 (m, 1 H), 1.38 (s, 9 H); ES-LCMS $(M+H)^+$ 447.3 RT = 3.58 min.

[527] Using the procedures of Intermediate Q and Examples 197-199, and substituting the appropriate starting materials, examples were similarly prepared and appear in Tables 16-17 below.

[528]

Table 16



Example No.	R^{21}	HPLC RT (min)	MS-ES [M+H]+
200	4-MeOPh-	2.98	421.3
201	4-CF_3Ph-	3.36	459.5
202		2.94	435.4
203	3,4-diMePh-	3.24	419.4
204	4-Br Ph	2.98	395.1
205	4-Et-Ph	3.34	419.3
206	H	2.4	315.2
207	4-(CO_2H)Ph-	2.66	435.2
208	4-MePh	3.06	405.3
209	2-MeOPh	2.97	421.3
210	3-CF_3Ph	3.24	459.3

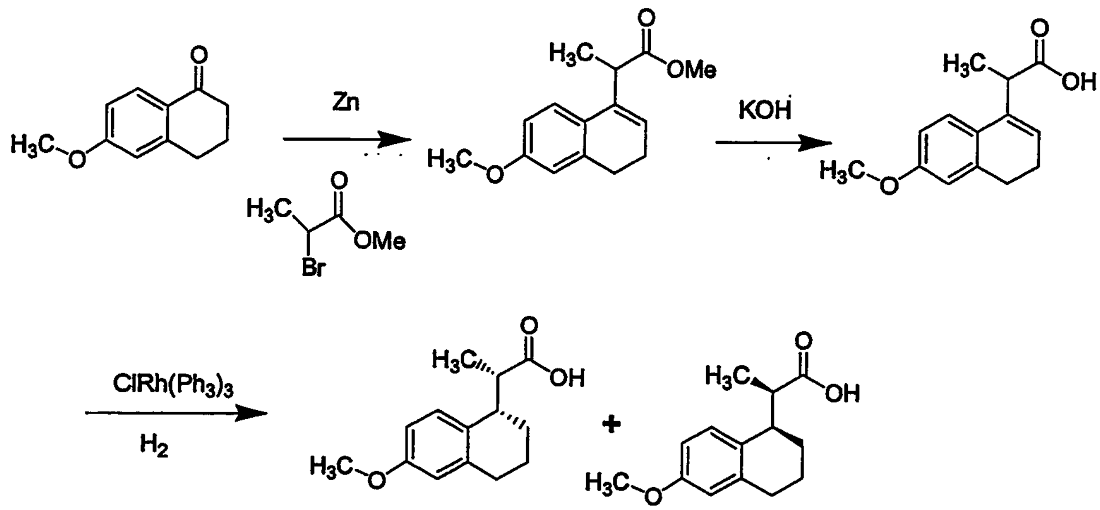
[529] **Table 17**

Example No.	IUPAC name
200	((1*S*)-5-{2-[4-(4-Methoxyphenyl)-3,5-dimethyl-1*H*-pyrazol-1-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid
201	[(1*S*)-5-(2-{3,5-Dimethyl-4-[4-(trifluoromethyl)phenyl]-1*H*-pyrazol-1-yl}ethoxy)-2,3-dihydro-1*H*-inden-1-yl]acetic acid
202	((1*S*)-5-{2-[4-(1,3-Benzodioxol-5-yl)-3,5-dimethyl-1*H*-pyrazol-1-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid
203	[(1*S*)-5-(2-{3,5-Dimethyl-4-[4-(trifluoromethyl)phenyl]-1*H*-pyrazol-1-yl}ethoxy)-2,3-dihydro-1*H*-inden-1yl]acetic acid
204	{(1*S*)-5-[2-(4-Bromo-3,5-dimethyl-1*H*-pyrazol-1-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic acid
205	((1*S*)-5-{2-[4-(4-Ethylphenyl)-3,5-dimethyl-1*H*-pyrazol-1-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid
206	{(1*S*)-5-[2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)ethoxy]-2,3-dihydro-1*H*-inden-1-yl}acetic acid
207	4-[1-(2-{[(1*S*)-1-(Carboxymethyl)-2,3-dihydro-1*H*-inden-5-yl]oxy}ethyl)-3,5-dimethyl-1*H*-pyrazol-4-yl]benzoic acid
208	((1*S*)-5-{2-[3,5-Dimethyl-4-(4-methylphenyl)-1*H*-pyrazol-1-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid
209	((1*S*)-5-{2-[4-(2-Methoxyphenyl)-3,5-dimethyl-1*H*-pyrazol-1-yl]ethoxy}-2,3-dihydro-1*H*-inden-1-yl)acetic acid
210	[(1S)-5-(2-{3,5-Dimethyl-4-[3-(trifluoromethyl)phenyl]-*1H*-pyrazol-1-yl}ethoxy)-2,3-dihydro-*1H*-inden-1-yl]acetic acid

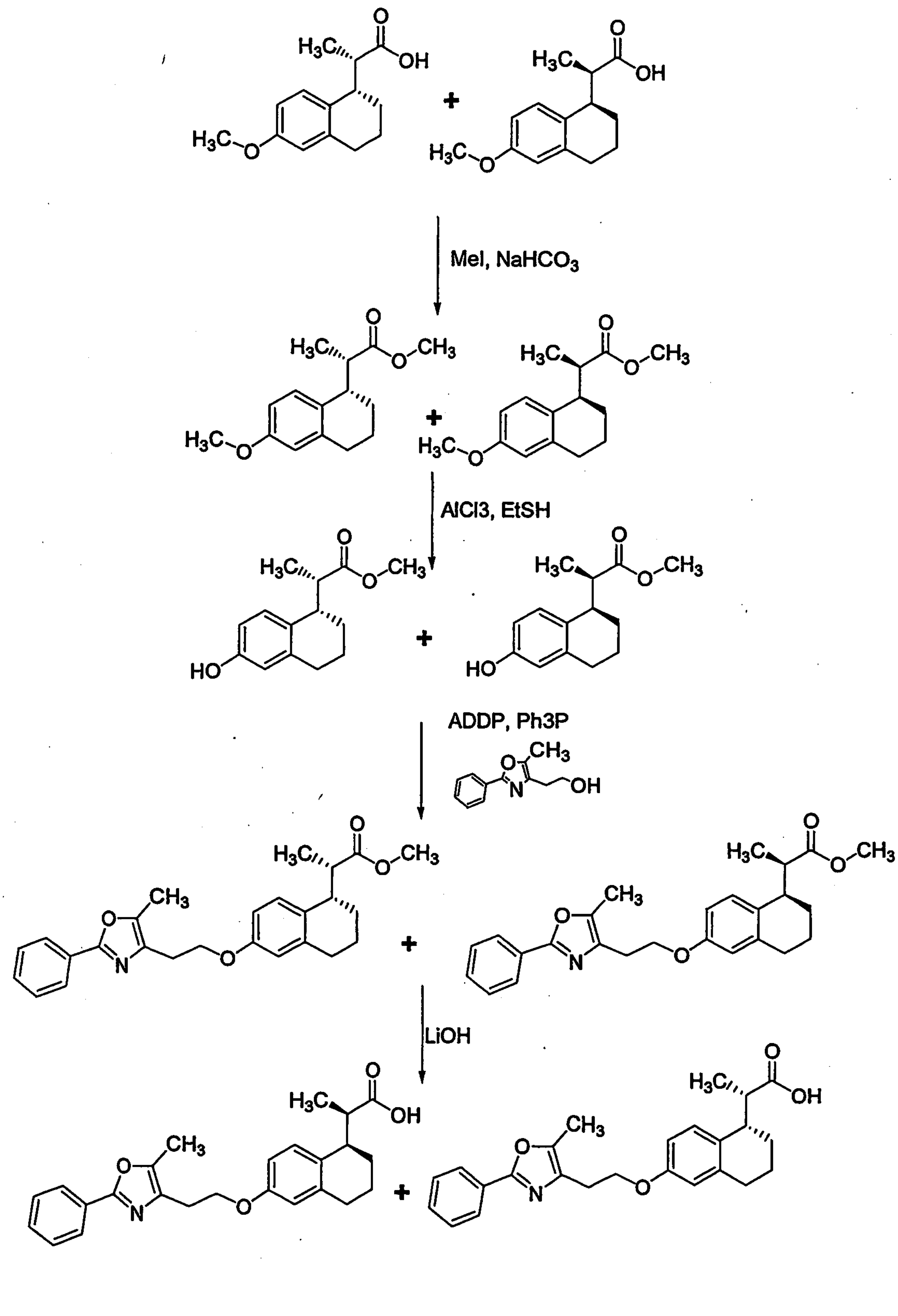
[530] Reaction Scheme 28 summarizes the synthetic methods utilized for the preparation of compounds of Formula (Id). These methods were used to prepare Example 211 as specifically described below.

Preparation of Tetrahydronaphthalenes

[531] **Reaction Scheme 28, part 1**

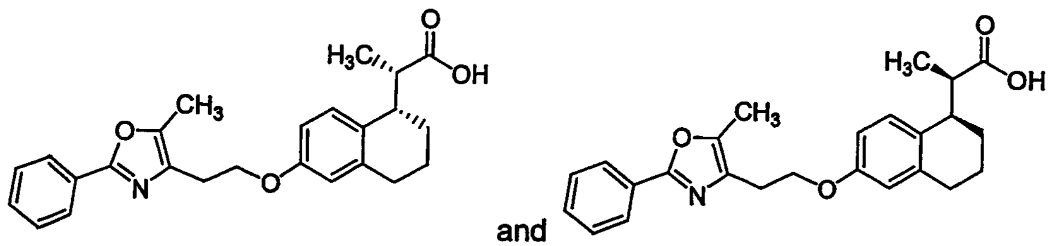


[532] **Reaction Scheme 28, Part 2**

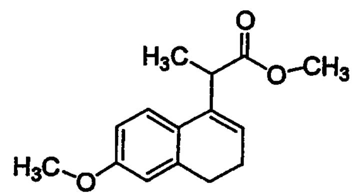


[533] **Example 211**

Preparation of (2*S*)-2-{(1*S*)-6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydro-1-naphthalenyl}propanoic acid and (2*R*)-2-{(1*R*)-6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydro-1-naphthalenyl}propanoic acid

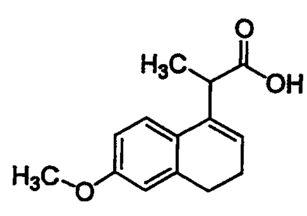


[534] Step 1: Preparation of methyl 2-(6-methoxy-3,4-dihydro-1-naphthalenyl)propanoate



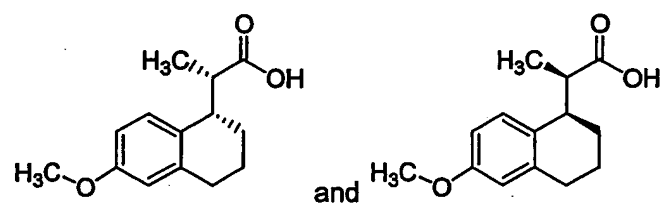
[535] Under argon atmosphere, a suspension of 6-methoxy-1-tetralone (4.0 g, 22.7 mmol) and Zn powder (Lancaster, 2.6 g, 39.7 mmol) in 100 mL anhydrous THF was stirred at 60°C, while a solution of methyl-2-bromopropionate (5.7 g, 34.0 mmol) in 20 mL anhydrous THF was added slowly through an addition funnel. After completion of the addition, the reaction was initiated with a small amount of active zinc species from a previous indanone Reformatsky run. The reaction mixture was stirred at 60°C for 4 h. Then the reaction mixture was cooled in an ice-water bath followed by slow addition of 150 mL of 1N HCl solution and extracted with EtOAc. The organic layer was washed with water until pH 6.0-7.0, then washed with saturated NaCl solution, and dried over Na_2SO_4, and concentrated *in vacuo*. Column chromatography (2.5% EtOAc/hexane) gave 1.7 g product, 30%. LC/MS retention time 3.06 min, ^{1}H NMR (CD_2Cl_2): δ 1.42 (d, 3H, α-methyl), 2.24~2.33 (m, 2H), 2.74 (t, 2H), 3.65 (s, 3H, ester), 3.73 (m,1H), 3.80 (s, 3H, methoxy), 5.91 (t, 1H, vinyl.), 6.74 (m, 2H), 7.20 (dd, 1H).

[536] Step 2: Preparation of 2-(6-methoxy-3,4-dihydro-1-naphthalenyl)propanoic acid



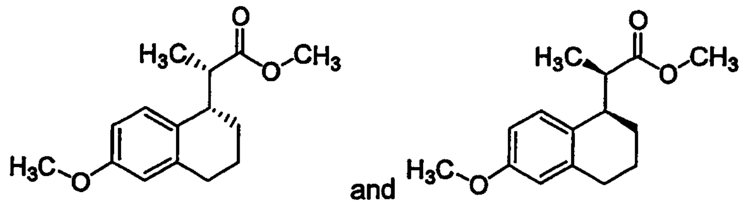
[537] To a solution of the ester prepared in Step 1 (3.1 g, 12.6 mmol) in 40 mL MeOH, was added a solution of KOH (2.0 g, 35.2 mmol) in 4 mL water. The reaction mixture was stirred at 65°C for 4 h. After cooling to rt, the solvents were removed at a reduced pressure. The residue was dissolved in 90 mL water, and then washed with CH_2Cl_2 (3 x 20 mL). The aqueous layer was cooled in an ice-water bath, and then acidified with conc. HCl to pH < 3.0. The product was extracted into 90 mL CH_2Cl_2, washed with water (3 x 15 mL), then dried over Na_2SO_4. The title product (2.6 g, 90%) was obtained as a light brown solid after solvent removal and vacuum dried. ^1H NMR (CD_2Cl_2): δ 1.42 (d, 3H, α-methyl), 2.24~2.34 (m, 2H), 2.75 (t, 2H), 3.75 (q, 1H, allylic), 3.79 (s, 3H, methoxy), 5.94 (t, 1H, vinyl.), 6.75 (m, 2H), 7.21 (dd, 1H).

[538] Step 3: Preparation of (2*S*)-2-[(1*S*)-6-methoxy-1,2,3,4-tetrahydro-1-naphthalenyl]propanoic acid and (2*R*)-2-[(1*R*)-6-methoxy-1,2,3,4-tetrahydro-1-naphthalenyl]propanoic acid



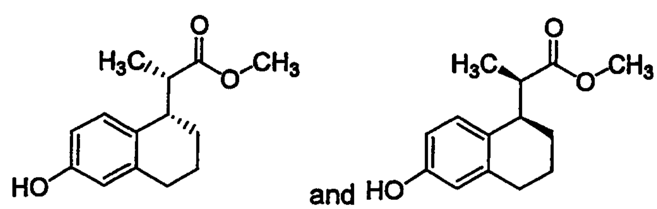
[539] A solution of the product obtained in Step 2 (2.5 g, 10.8 mmol), $ClRh(PPh_3)_3$ (0.5 g, 5% eq.), and triethylamine (1.8 g, 17.9 mmol) in EtOH (45 mL) and THF (5 mL) was shaken in a 500-mL pressure bottle under 60 psi H_2 for 40 h. The solvents were removed at a reduced pressure. The resulting mixture was stirred in 80 mL of 1N HCl solution and 80 mL CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined CH_2Cl_2 layers were washed with 1N HCl solution and stirred with 80 mL of 1N NaOH solution. The organic layer was extracted with 1N NaOH solution (3 x 30 mL). The combined aqueous layer was washed with CH_2Cl_2 (3 x 20 mL), and acidified (pH 2.0-3.0) by a slow addition of conc. HCl. The acidic mixture was extracted with CH_2Cl_2 (3 x 50 mL), and washed with water (2 x 30 mL) to pH 5.0-6.0. After washing with brine and drying over anhydrous Na_2SO_4, the solvent was evaporated under a reduced pressure. The product (2.1 g, 84%) was obtained as a yellow-tinged solid. TLC R_f (50% EtOAc/hexane) 0.5. ^1H NMR (d6-DMSO): δ 0.81 (d, 3H, α-methyl), 1.56 (m, 3H), 1.79 (m, 1H), 2.64 (t, 2H), 2.96 (m, 1H), 3.15 (m, 1H), 3.68 (s, 3H), 6.60 (d, 1H), 6.67 (dd, 1H), 7.11 (d, 1H), 12.15 (s, 1H, acid.)

[540] Step 4: Preparation of methyl (2*S*)-2-[(1*S*)-6-methoxy-1,2,3,4-tetrahydro-1-naphthalenyl]propanoate and methyl (2*R*)-2-[(1*R*)-6-methoxy-1,2,3,4-tetrahydro-1-naphthalenyl]propanoate



[541] A suspension of acid prepared in Step 3 (1.2 g, 5.1 mmol), $NaHCO_3$ (1.3 g, 15.4 mmol), CH_3I (1.5 g, 10.3 mmol) in 10 mL DMF was stirred under argon at rt for 18 h. TLC showed some starting material still remained. Adding 1.0 g CH_3I, and stirring for an additional 24 h at rt caused the reaction to run to completion. The reaction mixture was poured into 50 mL water, and extracted with EtOAc (3 x 30 mL). The organic layer was sequentially washed with water (3 x 20 mL), 1N NaOH solution (3 x 20 mL), water (2 x 20 mL), and brine and dried over Na_2SO_4. The product (1.25 g, 98%) was obtained as a brown oil after solvent removal and vacuum drying. TLC R_f (50% EtOAc/hexane) 0.8. ^1H NMR (CD_2Cl_2): δ 0.99 (d, 3H, α-methyl), 1.69 (m, 3H), 1.85 (m, 1H), 2.71(m, 2H), 2.97 (q, 1H), 3.21 (m, 1H), 3.61 (s, 3H, ester), 3.77 (s, 3H, methoxy), 6.61 (d, 1H), 6.67 (dd, 1H), 7.02 (d, 1H).

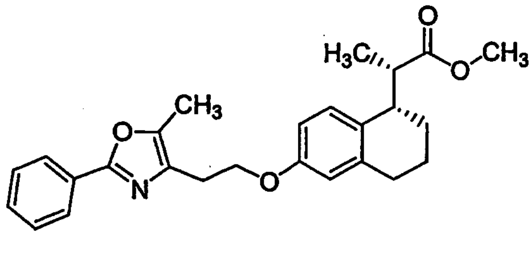
[542] Step 5: Preparation of methyl (2*S*)-2-[(1*S*)-6-hydroxy-1,2,3,4-tetrahydro-1-naphthalenyl]propanoate and methyl (2*R*)-2-[(1*R*)-6-hydroxy-1,2,3,4-tetrahydro-1-naphthalenyl]propanoate



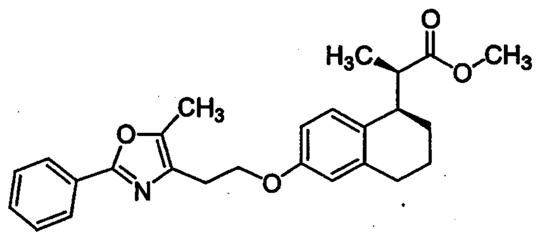
[543] To a cold solution (ice water bath) of the compound prepared in Step 4 (1.25 g, 5.0 mmol) in 15 mL CH_2Cl_2, was added $AlCl_3$ (3.4 g, 25.1 mmol) slowly under argon. The pot temperature was kept below 20°C, and the color of the reaction turned brown. EtSH (2.0 mL, 25.1 mmol) was added slowly via an addition funnel to the reaction mixture, and the internal temperature was kept below 15°C. After 3 h of stirring at below 20°C, the pot mixture was slowly poured into 100 mL ice water with a strong agitation. The organic layer was separated, and the aqueous layer was extracted with 100 mL CH_2Cl_2. The combined CH_2Cl_2 layers were washed with water (4 x 50 mL) until pH 6.0-7.0, and then dried over Na_2SO_4. Purified by column chromatography (15% EtOAc/hexane) gave 1.0 g

product, 85%, as an oil. TLC R_f = 0.7 (50% EtOAc/hexane). ^{1}H NMR (CD_2Cl_2): δ 1.00 (d, 3H, α-methyl), 1.66 (m, 3H), 1.83 (m, 1H), 2.69(m, 2H), 2.95 (q, 1H), 3.20 (m, 1H), 3.61 (s, 3H, ester), 4.87 (s, broad, 1H), 6.58 (m, 2H), 6.96 (dd, 1H).

[544] Step 6: Preparation of methyl (2*S*)-2-{(1*S*)-6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydro-1-naphthalenyl}propanoate and methyl (2*R*)-2-{(1*R*)-6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydro-1-naphthalenyl}propanoate

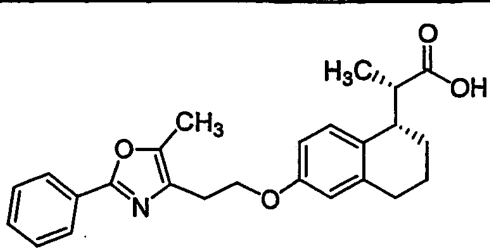


and

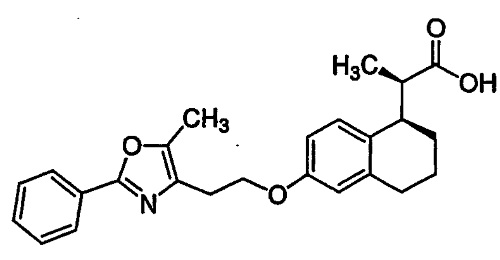


[545] A suspension of the product prepared in Step 5 (100 mg, 0.4 mmol), commercial 2-(5-methyl-2-phenyloxazol-4-yl)ethanol (104 mg, 0.5 mmol), ADDP (129 mg, 0.5 mmol), Ph_3P (135 mg, 0.5 mmol) in 2 mL anhydrous CH_2Cl_2 was stirred at rt under argon for 48 h. The residue was purified by column chromatography (5% EtOAc/hexane) to give 77 mg of the title product (35%). ^{1}H NMR (CD_2Cl_2): δ 0.98 (d, 3H, α-methyl), 1.67 (m, 3H), 1.84 (m, 1H), 2.40 (s, 3H, oxazole methyl), 2.69 (m, 2H), 2.95 (m, 1H), 3.03 (t, 2H), 3.20 (m, 1H), 3.60 (s, 3H, ester), 4.25 (t, 2H, methylene), 6.65 (m, 2H), 7.00 (d, 1H), 7.50 (m, 3H), 8.09 (m, 2H).

[546] Step 7: Preparation of (2*S*)-2-{(1*S*)-6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydro-1-naphthalenyl}propanoic acid and (2*R*)-2-{(1*R*)-6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-1,2,3,4-tetrahydro-1-naphthalenyl}propanoic acid



and



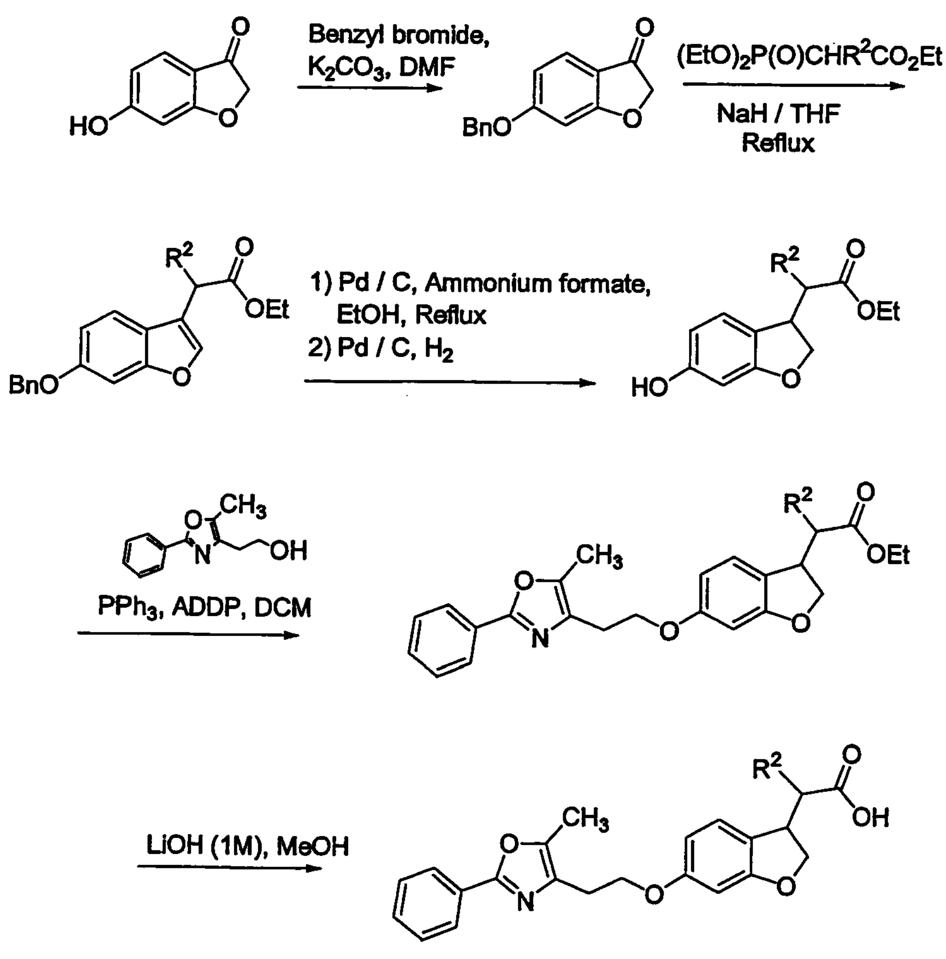
[547] To a solution of LiOH (1.22 mL, 1 M) and 5 mL MeOH, was added the ester prepared in Step 6 (64 mg, 0.15 mmol). This mixture was heated at 60°C for 18 h, and

the reaction mixture was cooled to rt, MeOH were removed at a reduced pressure. The residue was diluted with water until the solids dissolved. Conc. HCl solution was slowly added until pH 2.0-3.0, and the aqueous solution was extracted with EtOAc. The combined organic layer was washed with water, brine, and then dried over Na_2SO_4. The product (56 mg, 90%) was obtained as a white solid after solvent removal and vacuum drying. LC/MS retention time 3.51 min. ^{1}H NMR (CD_3OD): δ 0.88 (d, 3H, α-methyl), 1.62 (m, 3H), 1.80 (m, 1H), 2.33 (s, 3H, oxazole methyl), 2.63 (m, 2H), 2.95 (m, 3H), 3.22 (q, 1H, α-ester methine), 4.19 (t, 2H, methylene), 6.58 (d, 1H), 6.66 (dd, 1H), 7.07 (d, 1H), 7.44 (m, 3H), 7.93 (m, 2H).

[548] Reaction Scheme 29 summarizes the synthetic methods utilized for the preparation of compounds of Formula (Ie). These methods were used to prepare Examples 212-214 as specifically described below.

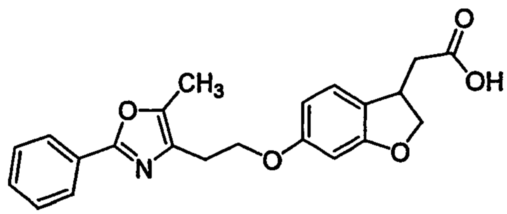
Preparation of Benzofurans

[549] **Reaction Scheme 29**

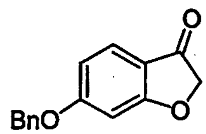


[550] Example 212

Preparation {6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1-benzofuran-3-ylacetic acid

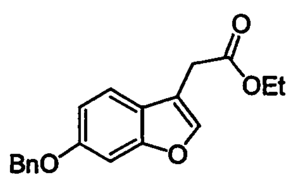


[551] Step 1: Preparation of 6-(benzyloxy)-1-benzofuran-3(2*H*)-one



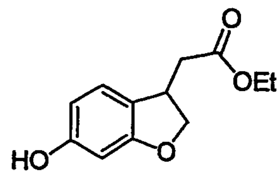
[552] Commercial 6-hydroxy-2*H*-benzofuran-3-one (4.4 g, 29.3 mmol) was dissolved in 50 mL dry DMF and potassium carbonate (7.36 g, 53.3 mmol) was added, followed by slow addition of benzyl bromide (3.8 mL, 32.0 mmol). The reaction was stirred at rt for 18 h, filtered, and the filtrate poured into 250 mL cold water. The red solid obtained was filtered, washed with water, and dried to give 7.0 g (98%) product, with properties matching the literature (*see, e.g.*, J. Med. Chem. 39:5035, 1996).

[553] Step 2: Preparation of ethyl [6-(benzyloxy)-1-benzofuran-3-yl]acetate



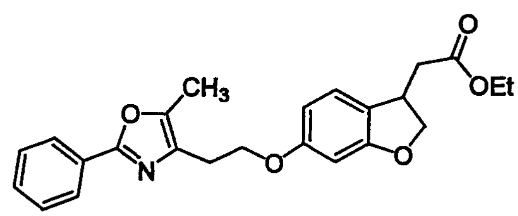
[554] Triethylphosphonoacetate (1.24 mL, 6.62 mmol) was added slowly to a stirred suspension of sodium hydride (0.17 g, 6.7 mmol) in 15 mL THF. After stirring at rt for 1 h, a solution of starting ketone (0.96 g, 4.2 mmol) in 10 mL THF was added, and the reaction mixture was heated to reflux overnight. Cooling, dilution with ethyl acetate, filtration through silica gel, and evaporation yielded material which was purified using flash chromatography (5% EtOAc/hexane) to give 0.28g (23%) product. TLC R_f (20% EtOAc/hexane) 0.45. ^{1}H NMR (CD_2Cl_2): δ 1.28 (t, 3H, methyl), 3.66 (s, 2H, methylene), 4.17 (q, 2H, ester methylene), 5.10 (s, 2H, benzyl methylene), 6.98 (dd, 1H), 7.10 (d, 1H), 7.42 (m, 6H), 7.56 (t, 1H).

[555] Step 3: Preparation of ethyl (6-hydroxy-2,3-dihydro-1-benzofuran-3-yl)acetate



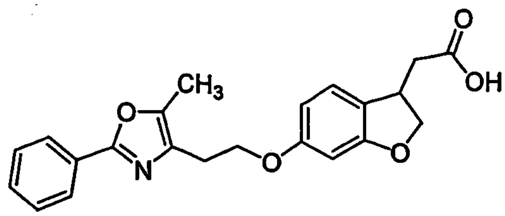
[556] Starting material (from Step 2, 0.24 g, 0.8 mmol) was taken up in 50 mL ethanol with palladium hydroxide on carbon (0.024g, 10% w/w). Ammonium formate (0.24 g, 3.8 mmol) was added, and the mixture was slowly warmed to 40°C. After 1 h, the reaction was heated to reflux for 48 h. Cooling, filtration, evaporation, and chromatography (20% EtOAc/hexane) gave 0.120 g material which proved to be a mixture of debenzylated alkane and alkene. This mixture was taken up in 10 mL ethanol with 0.01 g of 5% Pd/C catalyst, and hydrogenated under a balloon of hydrogen for 72 h. Filtration, evaporation, and chromatography as before gave 0.08 g of fully reduced product. R_f (50% EtOAc/hexane) 0.7. ^1H NMR (CD_2Cl_2): δ 1.25 (t, 3H, methyl), 2.55 (AB of ABX, 1H), 2.76 (AB of ABX, 1H), 3.80 (m, 1H), 4.16 (m, 2H, ester methylene). 4.25 (dd, 1H), 4.72 (t, 1H), 4.85 (s, broad, 1H), 6.31 (m, 2H), 7.0 (d, 1H).

[557] Step 4: Preparation of ethyl {6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1-benzofuran-3-yl}acetate



[558] Using the Mitsunobu coupling procedure as described above for Example 12, Step 5, reaction of 0.064 g starting phenol (Step 3), 2-(5-methyl-2-phenyloxazol-4-yl-ethanol (0.075 g), triphenylphosphine (0.107 g), and ADDP (0.103 g) in dichloromethane (5 mL) gave 0.060 g (50%) of product after chromatography using 10-18% EtOAc/hexane. ^1H NMR (CD_2Cl_2): δ 1.25 (t, 3H, methyl), 2.39 (s, 3H, oxazole methyl), 2.52 (AB of ABX, 1H), 2.71 (AB of ABX, 1H), 2.95 (t, 2H, methylene), 3.79 (m, 1H), 4.20 (m, 5H), 4.73 (t, 1H), 6.37 (d, 1H), 6.41 (dd, 1H), 7.03 (dd, 1H), 7.44 (m, 3H), 7.97 (m, 2H).

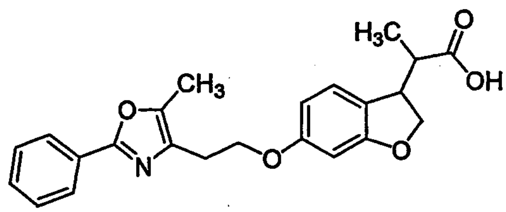
[559] Step 5: Preparation of {6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1-benzofuran-3-yl}acetic acid



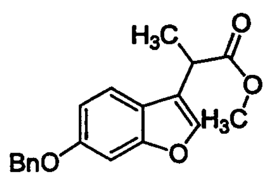
[560] The standard ester hydrolysis conditions as described above for Example 2 were used, starting from the ester from Step 4 (0.052 g) and using 1 mL 1M LiOH and 5 mL methanol; the yield was 0.040 g of product (83%) after workup and extraction. ^{1}H NMR (CD_3OD): δ 2.39 (s, 3H, oxazole methyl), 2.48 (AB of ABX, 1H), 2.70 (AB of ABX, 1H), 2.93 (t, 2H, methylene), 3.72 (m, 1H), 4.22 (m, 3H), 4.64 (t, 1H), 6.32 (s, 1H, aryl), 6.40 (d, 1H), 7.06 (d, 1H), 7.45 (m, 3H), 7.95 (m, 2H).

[561] **Example 213**

Preparation of 2-{6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1-benzofuran-3-yl}propanoic acid

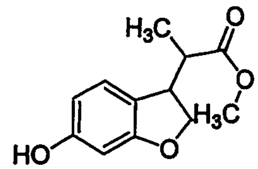


[562] Step 1: Preparation of methyl 2-[6-(benzyloxy)-1-benzofuran-3-yl]propanoate



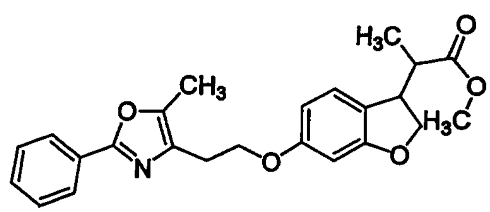
[563] The same Reformatsky procedure as described in Example 12, Step 1 was followed, using 2 g of starting ketone (obtained as in Step 1 of the preparation sequence above), 1.44 mL methyl 2-bromopropionate, and 1.09 g zinc dust in 100 mL toluene. Extractive workup and chromatography using 5% EtOAc/hexane gave 1.19 g product, (46%). TLC R_f (20% EtOAc/hexane) 0.52. ^{1}H NMR (CD_2Cl_2): δ 1.60 (d, 3H, α-methyl), 3.67 (s, 3H, methyl ester), 3.89 (q, 1H), 5.10 (s, 2H, benzyl methylene), 6.96 (dd, 1H), 7.08 (d, 1H), 7.43 (m, 7H).

[564] Step 2: Preparation of methyl 2-(6-hydroxy-2,3-dihydro-1-benzofuran-3-yl)propanoate



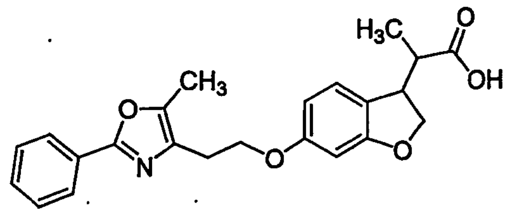
[565] The product of Step 1 (above) (1.16 g) was hydrogenated in 30 mL ethanol under balloon pressure (H_2 gas) with 0.01 g of 5% Pd/C catalyst. After five days, the mixture was filtered and evaporated. Chromatography using 30% EtOAc/hexane gave the phenol product, 0.65 g (75%). ^{1}H NMR (CD_2Cl_2): δ 1.08, 1.16 (each d, 3H, diastereomeric α-methyls), 2.66, 2.75 (each m, 1H, diastereomeric), 3.66, 3.74 (each m, 1H, diastereomeric), 3.68 (s, 3H, methyl ester), 4.36, 4.45 (each dd, 1H, diastereomeric), 4.59 (m, 1H), 4.97 (bs, 1H, OH), 6.28 (m 1H, aryl), 6.32 (m, 1H, aryl), 6.91, 7.00 (each d, 1H, diastereomeric aryls).

[566] Step 3: Preparation of methyl 2-{6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1-benzofuran-3-yl}propanoate



[567] Using the standard Mitsunobu coupling procedure as described in Step 5, Example 12, reaction of 2-(5-methyl-2-phenyloxazol-4-yl)ethanol (0.20 g), the product of Step 2 above (0.20 g), triphenylphosphine (0.28 g), and ADDP (0.277 g) in 5 mL dichloromethane, 0.30 g (82%) of product was obtained after chromatography using 25-35% EtOAc/hexane. ^{1}H NMR (CD_2Cl_2): δ 1.08, 1.17 (each d, 3H, diastereomeric α-methyls), 2.39 (s, 3H, oxazole methyl), 2.66, 2.75 (each m, 1H, diastereomeric), 2.95 (t, 2H), 3.65, 3.74 (each m, 1H, diastereomeric), 3.66 (s, 3H, methyl ester), 4.21 (t, 2H), 4.35, 4.43 (each dd, 2H, diastereomeric), 6.28 (m, 1H, aryl), 6.40 (m, 1H, aryl), 6.95, 7.01 (each d, 1H, diastereomeric aryls), 7.43 (m, 3H, aryls), 7.98 (m, 2H, aryls).

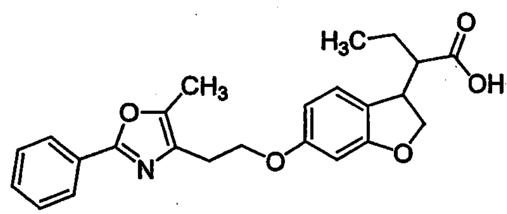
[568] Step 4: Preparation of 2-{6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1-benzofuran-3-yl}propanoic acid



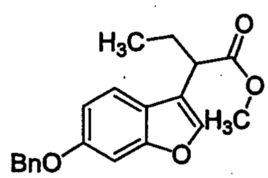
[569] Using the standard ester hydrolysis conditions and isolation procedure as described in Step 5, Example 212, 0.29 g of the starting ester from the previous step, 5.7 mL 1M LiOH, and 15 mL methanol yielded 0.25 g product (89%). LC/MS retention time 3.13 min. ^{1}H NMR (CD_3OD): δ 1.05, 1.10 (each d, 3H, diastereomeric α-methyls), 2.39 (s, 3H, oxazole methyl), 2.60, 2.68 (each m, 1H, diastereomeric), 2.97 (t, 2H), 3.65, 3.72 (each m, 1H, diastereomeric), 4.21 (t, 2H), 4.36, 4.40 (each dd, 2H, diastereomeric), 6.27 (m, 1H, aryl), 6.41 (m, 1H, aryl), 7.02, 7.06 (each d, 1H, diastereomeric aryls), 7.44 (m, 3H, aryls), 7.97 (m, 2H, aryls).

[570] **Example 214**

Preparation of 2-{6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1-benzofuran-3-yl}butanoic acid

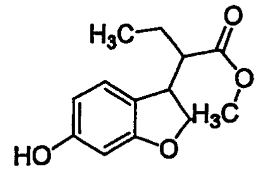


[571] Step 1: Preparation of methyl 2-[6-(benzyloxy)-1-benzofuran-3-yl]butanoate



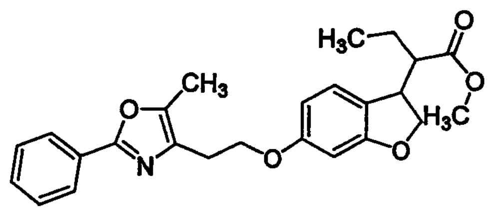
[572] The same Reformatsky procedure as described in Step 1, Example 12, was followed, using 1 g of starting ketone (obtained as in Step 1, Example 212), 0.72 mL methyl 2-bromobutyrate, and 0.54 g zinc dust in 35 mL toluene. Workup as described for Step 1, Example 12, followed by chromatography using 5% EtOAc/hexane gave 1.02 g (75%) product. TLC R_f (20% EtOAc/hexane) 0.55. ^{1}H NMR (CD_2Cl_2): δ 0.97 (d, 3H, methyl), 1.96 (m, 1H), 2.14 (m, 1H), 3.63 (s, 3H, methyl ester), 3.89 (q, 1H), 5.10 (s, 2H, benzyl methylene), 6.96 (dd, 1H), 7.09 (d, 1H), 7.44 (m, 7H).

[573] Step 2: Preparation of methyl 2-(6-hydroxy-2,3-dihydro-1-benzofuran-3-yl)butanoate



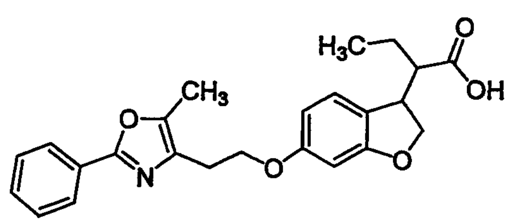
[574] The product of Step 1 (1.02 g) was hydrogenated under balloon pressure (H_2 gas) in 30 mL ethanol with 0.01g of 5% Pd/C catalyst for five days. Filtration and evaporation, followed by chromatography using 30% EtOAc/hexane gave 0.73 g (95%) product. ^{1}H NMR (CD_2Cl_2): δ 0.91 (2 t, 3H, diastereomeric methyls), 1.43, 1.63 (2 m, 2H, diastereomeric), 2.45, 2.48 (2 m, 1H, diastereomeric), 3.61 (m, 1H), 3.63, 3.70 (2 s, 3H, diastereomeric methyl esters), 4.45 (m, 2H), 6.26 (m, 2H, aryls), 6.88, 7.03 (2 d, 1H, diastereomeric aryls).

[575] Step 3: Preparation of methyl 2-{6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1-benzofuran-3-yl}butanoate



[576] Using the standard Mitsunobu coupling procedure as described in Example 12, Step 5, 0.19 g of the oxazolylethanol, 0.20 g of the product of Step 2, 0.27 g triphenylphosphine, and 0.26 g ADDP in 5 mL dichloromethane, provided 0.30 g (84%) of product after chromatography using 20-35% EtOAc/hexane. ^{1}H NMR (CD_2Cl_2): δ 0.89 (2 t, 3H, diastereomeric methyls), 1.65, 1.42 (2 m, 2H, diastereomeric), 2.39 (s, 3H, oxazole methyl), 2.48 (m, 1H), 2.97 (t, 2H, methylene), 3.60 (m, 1H), 3.61, 3.68 (s, 3H, two diastereomers of methyl ester), 4.20 (t, 2H, methylene), 4.40, 4.46 (dd, 1H, two diastereomeric methines), 6.40 (m, 2H, aryls), 6.90, 7.07 (d, 1H, diastereomeric aryl methines), 7.42 (m, 3H), 7.98 (m, 2H, aryls).

[577] Step 4: Preparation of 2-{6-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-2,3-dihydro-1-benzofuran-3-yl}butanoic acid



[579] The standard hydrolysis conditions as described in Example 2, using 0.29 g ester (from Step 3 above) in 5.5 mL 1M LiOH/15 mL MeOH, yielded 0.24 g (89%) of product. ^{1}H NMR (CD_3OD): δ 0.92 (mix of 2 t, 3H, diastereomeric methyls), 1.63, 1.42 (2 m, 2H, diastereomeric), 2.38 (s, 3H, oxazole methyl), 2.42 (m, 1H), 2.94 (t, 2H, methylene), 3.59 (m, 1H), 4.18 (t, 2H, methylene), 4.42 (AB of ABX, 1H), 4.50 (AB of ABX, 1H), 6.32 (s, 1H, aryl), 6.40 (dd, 1H, aryl), 7.01, 7.08 (each d, 1H, diastereomeric aryls), 7.44 (m, 3H, aryls), 7.96 (m, 2H, aryls).

[580] The compounds of the present invention provide a new therapy for patients with, for example, metabolic disorders such as those resulting from decreased endogenous insulin secretion, in particular type 2 diabetics, or for patients with impaired glucose tolerance, a prediabetic state that has a mild alteration in insulin secretion. In addition, the compounds of the present invention may be useful in the prevention and/or treatment of type 1 diabetes, gestational diabetes, maturity-onset diabetes of the young (MODY), latent autoimmune diabetes adult (LADA), and associated diabetic dyslipidemia and other diabetic complications, as well as hyperglycemia, hyperinsulinemia, impaired glucose tolerance, impaired fasting glucose, dyslipidemia, hypertriglyceridemia, Syndrome X, and insulin resistance.

[581] The compounds of the present invention may also be utilized in the prevention and/or treatment of obesity (e.g., regulation of appetite and food intake); atherosclerotic disease, hyperlipidemia, hypercholesteremia, low HDL levels, hypertension, cardiovascular disease (including atherosclerosis, coronary heart disease, coronary artery disease, and hypertension), cerebrovascular disease and peripheral vessel disease; and for the treatment of lupus, polycystic ovary syndrome, carcinogenesis, and hyperplasia.

[582] The compounds of the present invention are also useful for treating physiological disorders related to, for example, cell differentiation to produce lipid accumulating cells, regulation of insulin sensitivity and blood glucose levels, which are involved in hypoglycemia/hyperinsulinism resulting from, for example, abnormal pancreatic beta cell function, insulin secreting tumors and /or autoimmune hypoglycemia due to autoantibodies to insulin, autoantibodies to the insulin receptor, or autoantibodies that are stimulatory to pancreatic beta cells), macrophage differentiation which leads to the formation of atherosclerotic plaques, inflammatory response, carcinogenesis, hyperplasia, adipocyte gene expression, adipocyte differentiation, reduction in the pancreatic β-cell mass, insulin secretion, tissue sensitivity to insulin, liposarcoma cell growth, polycystic ovarian disease, chronic anovulation, hyperandrogenism, progesterone production,

steroidogenesis, redox potential and oxidative stress in cells, nitric oxide synthase (NOS) production, increased gamma glutamyl transpeptidase, catalase, plasma triglycerides, HDL and LDL cholesterol levels and the like.

[583] Particularly useful compounds of the present invention are those with efficacy in lowering blood glucose concentration and serum triglyceride levels and raising serum HDL cholesterol levels.

[584] Compounds of the invention may also be used in methods of the invention to treat secondary causes of diabetes (Expert Committee on Classification of Diabetes Mellitus, Diabetes Care 22 (Supp. 1):S5, 1999). Such secondary causes include glucocorticoid excess, growth hormone excess, pheochromocytoma, and drug-induced diabetes. Drugs that may induce diabetes include, but are not limited to, pyriminil, nicotinic acid, glucocorticoids, phenytoin, thyroid hormone, β-adrenergic agents, α-interferon, and drugs used to treat HIV infection.

[585] Therefore, the compounds of this invention are expected to be valuable as therapeutic agents. Accordingly, an embodiment of this invention includes a method of treating the various conditions identified above in a mammal which comprises administering to said mammal a composition containing an amount of the compound of the invention that is effective in treating the target condition.

[586] A compound of the invention may be administered alone or in combination with one or more additional hypoglycemic agents. Combination therapy includes administration of a single pharmaceutical dosage formulation which contains a compound of the invention and one or more additional hypoglycemic agents, as well as administration of the compound of the invention and each additional hypoglycemic agents in its own separate pharmaceutical dosage formulation. For example, a compound of the invention and hypoglycemic agent can be administered to the patient together in a single oral dosage composition such as a tablet or capsule, or each agent administered in separate oral dosage formulations.

[587] Where separate dosage formulations are used, the compound of the invention and one or more additional hypoglycemic agents can be administered at essentially the same time, i.e., concurrently, or at separately staggered times, i.e., sequentially.

[588] For example, the compound of the invention may also be administered in combination with other known therapies for the treatment of diabetes, including PPAR agonists, sulfonylurea drugs, non-sulfonylurea secretagogues, α-glucosidase inhibitors, insulin sensitizers, insulin secretagogues, hepatic glucose output lowering compounds,

insulin and anti-obesity drugs. Such therapies may be administered prior to, concurrently with or following administration of the compounds of the invention. Insulin includes both long and short acting forms and formulations of insulin. PPAR agonist may include agonists of any of the PPAR subunits or combinations thereof. For example, PPAR agonist may include agonists of PPAR-α, PPAR-γ, PPAR-δ or any combination of two or three of the subunits of PPAR. PPAR agonists include, for example, rosiglitazone and pioglitazone. Sulfonylurea drugs include, for example, glyburide, glimepiride, chlorpropamide, and glipizide. α-glucosidase inhibitors that may be useful in treating diabetes when administered with a compound of the invention include acarbose, miglitol and voglibose. Insulin sensitizers that may be useful in treating diabetes include thiazolidinediones and non-thiazolidinediones. Hepatic glucose output lowering compounds that may be useful in treating diabetes when administered with a compound of the invention include metformin, such as Glucophage and Glucophage XR. Insulin secretagogues that may be useful in treating diabetes when administered with a compound of the invention include sulfonylurea (such as acetohexamide, chloropropamide, tolazamide, tolbutamide, glyburide, glipizide, glyclazide, repaglinide, nateglinide) and non-sulfonylurea drugs: GLP-1, GIP, secretin, nateglinide, meglitinide, repaglinide, glibenclamide, glimepiride, chlorpropamide, glipizide. GLP-1 includes derivatives of GLP-1 with longer half-lives than native GLP-1, such as, for example, fatty-acid derivatized GLP-1 and exendin. In one embodiment of the invention, compounds of the invention are used in combination with insulin secretagogues to increase the sensitivity of pancreatic β-cells to the insulin secretagogue.

[589] Compounds of the invention may also be used in methods of the invention in combination with anti-obesity drugs. Anti-obesity drugs include β-3 agonists (such as CL-316, 243), CB-1 antagonists, appetite suppressants, such as, for example, sibutramine (Meridia), and lipase inhibitors, such as, for example, orlistat (Xenical).

[590] Compounds of the invention may also be used in methods of the invention in combination with drugs commonly used to treat lipid disorders in diabetic patients. Such drugs include, but are not limited to, HMG-CoA reductase inhibitors, nicotinic acid, bile acid sequestrants, and fibric acid derivatives. Compounds of the invention may also be used in combination with anti-hypertensive drugs, such as, for example, β-blockers and ACE inhibitors.

[591] The compounds of the invention may also be utilized, in free base form or in compositions, in research and diagnostics, or as analytical reference standards, and the like, which are well known in the art. Therefore, the present invention includes

compositions which are comprised of an inert carrier and an effective amount of a compound of the invention, or a salt or ester thereof. An inert carrier is any material which does not interact with the compound to be carried and which lends support, means of conveyance, bulk, traceable material, and the like to the compound to be carried. An effective amount of compound is that amount which produces a result or exerts an influence on the particular procedure being performed.

Pharmaceutical Compositions

[592] As used herein, various terms are defined below.

[593] When introducing elements of the present invention or the preferred embodiment(s) thereof, the articles "a," "an," "the," and "said" are intended to mean that there are one or more of the elements. The terms "comprising," "including," and "having" are intended to be inclusive and mean that there may be additional elements other than the listed elements.

[594] The term "subject" as used herein includes mammals (e.g., humans and animals).

[595] The term "treatment" includes any process, action, application, therapy, or the like, wherein a subject, including a human being, is provided medical aid with the object of improving the subject's condition, directly or indirectly, or slowing the progression of a condition or disorder in the subject.

[596] The term "combination therapy" or "co-therapy" means the administration of two or more therapeutic agents to treat a diabetic condition and/or disorder. Such administration encompasses co-administration of two or more therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each active ingredient. In addition, such administration encompasses use of each type of therapeutic agent in a sequential manner.

[597] The phrase "therapeutically effective" means the amount of each agent administered that will achieve the goal of improvement in a diabetic condition or disorder severity, while avoiding or minimizing adverse side effects associated with the given therapeutic treatment.

[598] The term "pharmaceutically acceptable" means that the subject item is appropriate for use in a pharmaceutical product.

[599] Based on well known assays used to determine the efficacy for treatment of conditions identified above in mammals, and by comparison of these results with the results of known medicaments that are used to treat these conditions, the effective dosage of the compounds of this invention can readily be determined for treatment of each desired indication. The amount of the active ingredient to be administered in the treatment of one of these conditions can vary widely according to such considerations as the particular compound and dosage unit employed, the mode of administration, the period of treatment, the age and sex of the patient treated, and the nature and extent of the condition treated.

[600] Compounds of the present invention may be administered as a compound *per se*. Alternatively, the compounds may be administered with an acceptable carrier in the form of a pharmaceutical composition. The pharmaceutically acceptable carrier must be compatible with the other ingredients of the composition and must not be intolerably deleterious to the recipient. The carrier can be a solid or a liquid, or both, and preferably is formulated with the compound as a unit-dose composition, for example, a tablet, which can contain from about 0.05% to about 95% by weight of the active compound(s) based on a total weight of the dosage form. Other pharmacologically active substances can also be present, including other compounds useful in the treatment of a diabetic condition.

[601] Compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a therapeutically effective dose for the treatment intended. The compounds may, for example, be administered orally, sublingually, nasally, pulmonary, mucosally, parenterally, intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically. Unit dose formulations, particularly orally administrable unit dose formulations such as tablets or capsules, generally contain, for example, from about 0.001 to about 500 mg, preferably from about 0.005 mg to about 100 mg, and more preferably from about 0.01 to about 50 mg, of the active ingredient and may be administered one or more times per day. In the case of pharmaceutically acceptable salts, the weights indicated above for the active ingredient refer to the weight of the pharmaceutically active ion derived from the salt.

[602] The total amount of the active ingredient to be administered may generally range from about 0.001 mg/kg to about 200 mg/kg, and preferably from about 0.01 mg/kg to about 200 mg/kg body weight per day. The daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous, and parenteral injections, and use of

infusion techniques may be from about 0.01 to about 200 mg/kg. The daily rectal dosage regimen may be from 0.01 to 200 mg/kg of total body weight. The transdermal concentration may be that required to maintain a daily dose of from 0.01 to 200 mg/kg.

[603] Of course, the specific initial and continuing dosage regimen to prevent, treat, give relief from, or ameliorate a diabetic condition or disorder, or to otherwise protect against or treat a diabetic condition for each patient will vary according to the nature and severity of the condition as determined by the attending diagnostician, the activity of the specific compound employed, the age of the patient, the diet of the patient, time of administration, route of administration, rate of excretion of the drug, drug combinations, pharmacological considerations such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized, and whether the compound is administered with other active ingredients, and the like. The desired mode of treatment and number of doses of a compound may be ascertained by those skilled in the art using conventional treatment tests.

[604] The compounds of this invention may be utilized to achieve the desired pharmacological effect by administration to a patient in need thereof in an appropriately formulated pharmaceutical composition. A patient, for the purpose of this invention, is a mammal, including a human, in need of treatment for a particular condition or disease. Therefore, the present invention includes pharmaceutical compositions which are comprised of a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound identified by the methods described herein, or a pharmaceutically acceptable salt or ester thereof. A pharmaceutically acceptable carrier is any carrier that is relatively non-toxic and innocuous to a patient at concentrations consistent with effective activity of the active ingredient so that any side effects ascribable to the carrier do not vitiate the beneficial effects of the active ingredient. A pharmaceutically effective amount of a compound is that amount which produces a result or exerts an influence on the particular condition being treated. The compounds identified by the methods described herein may be administered with a pharmaceutically-acceptable carrier using any effective conventional dosage unit forms, including, for example, immediate and timed release preparations, orally, parenterally, topically, or the like.

[605] For oral administration, the compounds may be formulated into solid or liquid preparations such as, for example, capsules, pills, tablets, troches, lozenges, melts, powders, solutions, pastes, syrups, suspensions, or emulsions, and may be prepared according to methods known to the art for the manufacture of pharmaceutical compositions. The solid unit dosage forms may be a capsule that can be of the ordinary

hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers such as lactose, sucrose, calcium phosphate, and corn starch. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient.

[606] In another embodiment, the compounds of this invention may be tableted with conventional tablet bases such as lactose, sucrose, and cornstarch in combination with binders such as acacia, cornstarch, or gelatin; disintegrating agents intended to assist the break-up and dissolution of the tablet following administration such as potato starch, alginic acid, corn starch, and guar gum; lubricants intended to improve the flow of tablet granulation and to prevent the adhesion of tablet material to the surfaces of the tablet dies and punches, for example, talc, stearic acid, or magnesium, calcium or zinc stearate; dyes; coloring agents; and flavoring agents intended to enhance the aesthetic qualities of the tablets and make them more acceptable to the patient. Suitable excipients for use in oral liquid dosage forms include diluents such as water and alcohols, for example, ethanol, benzyl alcohol, and polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent, or emulsifying agent. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance tablets, pills or capsules may be coated with shellac, sugar or both.

[607] Dispersible powders and granules are suitable for the preparation of an aqueous suspension. They provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, those sweetening, flavoring and coloring agents described above, may also be present.

[608] The pharmaceutical compositions of this invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil such as liquid paraffin or a mixture of vegetable oils. Suitable emulsifying agents may be (1) naturally occurring gums such as gum acacia and gum tragacanth, (2) naturally occurring phosphatides such as soy bean and lecithin, (3) esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan monooleate, and (4) condensation products of said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

[609] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil such as, for example, arachis oil, olive oil, sesame oil, or coconut oil; or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as, for example, beeswax, hard paraffin, or cetyl alcohol. The suspensions may also contain one or more preservatives, for example, ethyl or *n*-propyl p-hydroxybenzoate; one or more coloring agents; one or more flavoring agents; and one or more sweetening agents such as sucrose or saccharin.

[610] Syrups and elixirs may be formulated with sweetening agents such as, for example, glycerol, propylene glycol, sorbitol, or sucrose. Such formulations may also contain a demulcent, and preservative, flavoring and coloring agents.

[611] Oral delivery of the compounds of the present invention can include formulations well known in the art to provide immediate delivery or prolonged or sustained delivery of a drug to the gastrointestinal tract by any number of mechanisms. Immediate delivery formulations include, but are not limited to, oral solutions, oral suspensions, fast-dissolving tablets or capsules, sublingual tablets, disintegrating tablets and the like. Prolonged or sustained delivery formulations include, but are not limited to, pH sensitive release of the active ingredient from the dosage form based on the changing pH of the small intestine, slow erosion of a tablet or capsule, retention in the stomach based on the physical properties of the formulation, bioadhesion of the dosage form to the mucosal lining of the intestinal tract, or enzymatic release of the active drug from the dosage form. The intended effect is to extend the time period over which an active drug molecule is delivered to the site of action by manipulation of the dosage form. Thus, enteric-coated and enteric-coated controlled release formulations may be used in methods of the present invention. Suitable enteric coatings include cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethyl-cellulose phthalate and anionic polymers of methacrylic acid and methacrylic acid methyl ester.

[612] Pharmaceutical compositions can be prepared by any suitable method of pharmacy, which includes the step of bringing into association, the a compound of the present invention and the carrier (which can constitute one or more accessory ingredients). In general, the compositions are prepared by uniformly and intimately admixing the compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the product. For example, a tablet can be prepared by compressing or molding a powder or granules of the compounds, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules

optionally mixed with a binder, lubricant, inert diluent and/or surface active/dispersing agent(s). Molded tablets can be made, for example, by molding the powdered compound in a suitable machine.

[613] Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

[614] Pharmaceutical compositions suitable for buccal (sub-lingual) administration include lozenges comprising a compound of the present invention in a flavored base, usually sucrose, and acacia or tragacanth, and pastilles comprising the compounds in an inert base such as gelatin and glycerin or sucrose and acacia.

[615] The compounds of this invention may also be administered parenterally, that is, subcutaneously, intravenously, intramuscularly, or interperitoneally, as injectable dosages of the compound in a physiologically acceptable diluent with a pharmaceutical carrier which may be a sterile liquid or mixture of liquids such as water, saline, aqueous dextrose and related sugar solutions; an alcohol such as ethanol, isopropanol, or hexadecyl alcohol; glycols such as propylene glycol or polyethylene glycol; glycerol ketals such as 2,2-dimethyl-1,1-dioxolane-4-methanol, ethers such as poly(ethyleneglycol) 400; an oil; a fatty acid; a fatty acid ester or glyceride; or an acetylated fatty acid glyceride with or without the addition of a pharmaceutically acceptable surfactant such as a soap or a detergent, suspending agent such as pectin, carbomers, methycellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agent and other pharmaceutical adjuvants.

[616] Illustrative of oils which can be used in the parenteral formulations of this invention are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, sesame oil, cottonseed oil, corn oil, olive oil, petrolatum, and mineral oil. Suitable fatty acids include oleic acid, stearic acid, and isostearic acid. Suitable fatty acid esters are, for example, ethyl oleate and isopropyl myristate. Suitable soaps include fatty alkali metal, ammonium, and triethanolamine salts and suitable detergents include cationic detergents, for example, dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates; anionic detergents, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates; nonionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and

polyoxyethylenepolypropylene copolymers; and amphoteric detergents, for example, alkyl-beta-aminopropionates, and 2-alkylimidazoline quarternary ammonium salts, as well as mixtures.

[617] The parenteral compositions of this invention may typically contain from about 0.5% to about 25% by weight of the active ingredient in solution. Preservatives and buffers may also be used advantageously. In order to minimize or eliminate irritation at the site of injection, such compositions may contain a non-ionic surfactant having a hydrophile-lipophile balance (HLB) of from about 12 to about 17. The quantity of surfactant in such formulation ranges from about 5% to about 15% by weight. The surfactant can be a single component having the above HLB or can be a mixture of two or more components having the desired HLB.

[618] Illustrative of surfactants used in parenteral formulations are the class of polyethylene sorbitan fatty acid esters, for example, sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol.

[619] The pharmaceutical compositions may be in the form of sterile injectable aqueous suspensions. Such suspensions may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents such as, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents which may be a naturally occurring phosphatide such as lecithin, a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate, a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadecaethyleneoxycetanol, a condensation product of ethylene oxide with a partial ester derived form a fatty acid and a hexitol such as polyoxyethylene sorbitol monooleate, or a condensation product of an ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride, for example polyoxyethylene sorbitan monooleate.

[620] The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Diluents and solvents that may be employed are, for example, water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile fixed oils are conventionally employed as solvents or suspending media. For this purpose, any bland, fixed oil may be employed including synthetic mono or diglycerides. In addition, fatty acids such as oleic acid may be used in the preparation of injectables.

[621] A composition of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions may be prepared by mixing the drug with a suitable non-irritation excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such material are, for example, cocoa butter and polyethylene glycol.

[622] Another formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art (*see*, e.g., U.S. Patent No. 5,023,252, incorporated herein by reference). Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

[623] It may be desirable or necessary to introduce the pharmaceutical composition to the patient via a mechanical delivery device. The construction and use of mechanical delivery devices for the delivery of pharmaceutical agents is well known in the art. For example, direct techniques for administering a drug directly to the brain usually involve placement of a drug delivery catheter into the patient's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of agents to specific anatomical regions of the body, is described in U.S. Patent No. 5,011,472, incorporated herein by reference.

[624] The compositions of the invention may also contain other conventional pharmaceutically acceptable compounding ingredients, generally referred to as carriers or diluents, as necessary or desired. Any of the compositions of this invention may be preserved by the addition of an antioxidant such as ascorbic acid or by other suitable preservatives. Conventional procedures for preparing such compositions in appropriate dosage forms can be utilized.

[625] Commonly used pharmaceutical ingredients which may be used as appropriate to formulate the composition for its intended route of administration include: acidifying agents, for example, but are not limited to, acetic acid, citric acid, fumaric acid, hydrochloric acid, nitric acid; and alkalinizing agents such as, but are not limited to, ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium hydroxide, triethanolamine, trolamine.

[626] Other pharmaceutical ingredients include, for example, but are not limited to, adsorbents (e.g., powdered cellulose and activated charcoal); aerosol propellants (e.g., carbon dioxide, CCl_2F_2, F_2ClC-$CClF_2$ and $CClF_3$); air displacement agents (e.g., nitrogen and argon); antifungal preservatives (e.g., benzoic acid, butylparaben, ethylparaben, methylparaben, propylparaben, sodium benzoate); antimicrobial preservatives (e.g., benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate and thimerosal); antioxidants (e.g., ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorus acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite); binding materials (e.g., block polymers, natural and synthetic rubber, polyacrylates, polyurethanes, silicones and styrene-butadiene copolymers); buffering agents (e.g., potassium metaphosphate, potassium phosphate monobasic, sodium acetate, sodium citrate anhydrous and sodium citrate dihydrate); carrying agents (e.g., acacia syrup, aromatic syrup, aromatic elixir, cherry syrup, cocoa syrup, orange syrup, syrup, corn oil, mineral oil, peanut oil, sesame oil, bacteriostatic sodium chloride injection and bacteriostatic water for injection); chelating agents (e.g., edetate disodium and edetic acid); colorants (e.g., FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel and ferric oxide red); clarifying agents (e.g., bentonite); emulsifying agents (but are not limited to, acacia, cetomacrogol, cetyl alcohol, glyceryl monostearate, lecithin, sorbitan monooleate, polyethylene 50 stearate); encapsulating agents (e.g., gelatin and cellulose acetate phthalate); flavorants (e.g., anise oil, cinnamon oil, cocoa, menthol, orange oil, peppermint oil and vanillin); humectants (e.g., glycerin, propylene glycol and sorbitol); levigating agents (e.g., mineral oil and glycerin); oils (e.g., arachis oil, mineral oil, olive oil, peanut oil, sesame oil and vegetable oil); ointment bases (e.g., lanolin, hydrophilic ointment, polyethylene glycol ointment, petrolatum, hydrophilic petrolatum, white ointment, yellow ointment, and rose water ointment); penetration enhancers (transdermal delivery) (e.g., monohydroxy or polyhydroxy alcohols, saturated or unsaturated fatty alcohols, saturated or unsaturated fatty esters, saturated or unsaturated dicarboxylic acids, essential oils, phosphatidyl derivatives, cephalin, terpenes, amides, ethers, ketones and ureas); plasticizers (e.g., diethyl phthalate and glycerin); solvents (e.g., alcohol, corn oil, cottonseed oil, glycerin, isopropyl alcohol, mineral oil, oleic acid, peanut oil, purified water, water for injection, sterile water for injection and sterile water for irrigation); stiffening agents (e.g., cetyl alcohol, cetyl esters wax, microcrystalline wax, paraffin, stearyl alcohol, white wax and yellow wax); suppository bases (e.g., cocoa butter

and polyethylene glycols (mixtures)); surfactants (e.g., benzalkonium chloride, nonoxynol 10, oxtoxynol 9, polysorbate 80, sodium lauryl sulfate and sorbitan monopalmitate); suspending agents (e.g., agar, bentonite, carbomers, carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, methylcellulose, tragacanth and veegum); sweetening e.g., aspartame, dextrose, glycerin, mannitol, propylene glycol, saccharin sodium, sorbitol and sucrose); tablet anti-adherents (e.g., magnesium stearate and talc); tablet binders (e.g., acacia, alginic acid, carboxymethylcellulose sodium, compressible sugar, ethylcellulose, gelatin, liquid glucose, methylcellulose, povidone and pregelatinized starch); tablet and capsule diluents (e.g., dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sodium carbonate, sodium phosphate, sorbitol and starch); tablet coating agents (e.g., liquid glucose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, cellulose acetate phthalate and shellac); tablet direct compression excipients (e.g., dibasic calcium phosphate); tablet disintegrants (e.g., alginic acid, carboxymethylcellulose calcium, microcrystalline cellulose, polacrillin potassium, sodium alginate, sodium starch glycollate and starch); tablet glidants (e.g., colloidal silica, corn starch and talc); tablet lubricants (e.g., calcium stearate, magnesium stearate, mineral oil, stearic acid and zinc stearate); tablet/capsule opaquants (e.g., titanium dioxide); tablet polishing agents (e.g., carnuba wax and white wax); thickening agents (e.g., beeswax, cetyl alcohol and paraffin); tonicity agents (e.g., dextrose and sodium chloride); viscosity increasing agents (e.g., alginic acid, bentonite, carbomers, carboxymethylcellulose sodium, methylcellulose, povidone, sodium alginate and tragacanth); and wetting agents (e.g., heptadecaethylene oxycetanol, lecithins, polyethylene sorbitol monooleate, polyoxyethylene sorbitol monooleate, and polyoxyethylene stearate).

[627] The total daily dose of an active ingredient can be administered to the patient in a single dose, or in multiple subdoses. Typically, subdoses can be administered two to six times per day, preferably two to four times per day, and even more preferably two to three times per day. Doses can be in immediate release form or sustained release form sufficiently effective to obtain the desired control over the diabetic condition.

[628] The compounds identified by the methods described herein may be administered as the sole pharmaceutical agent or in combination with one or more other pharmaceutical agents where the combination causes no unacceptable adverse effects. For example, the compounds of this invention can be combined with known anti-obesity,

or with known antidiabetic or other indication agents, and the like, as well as with admixtures and combinations thereof.

[629] The compounds identified by the methods described herein may also be utilized, in free base form or in compositions, in research and diagnostics, or as analytical reference standards, and the like. Therefore, the present invention includes compositions which are comprised of an inert carrier and an effective amount of a compound identified by the methods described herein, or a salt or ester thereof. An inert carrier is any material which does not interact with the compound to be carried and which lends support, means of conveyance, bulk, traceable material, and the like to the compound to be carried. An effective amount of compound is that amount which produces a result or exerts an influence on the particular procedure being performed.

[630] The compounds of the present invention may also be administered as the pharmaceutically acceptable salt, protected acid, conjugate acid, tautomer, prodrug or stereoisomer of a compound. Tautomers include, for example, hydroxy tautomers. Protected acids include, but are not limited to, protected acids such as esters, hydroxyamino derivatives, amides and sulfonamides. Formation of prodrugs is well known in the art in order to enhance the properties of the parent compound; such properties include solubility, absorption, biostability and release time (see "*Pharmaceutical Dosage Form and Drug Delivery Systems*" (Sixth Edition), edited by Ansel et al., publ. by Williams & Wilkins, pgs. 27-29, (1995) which is hereby incorporated by reference). Commonly used prodrugs are designed to take advantage of the major drug biotransformation reactions and are also to be considered within the scope of the invention. Major drug biotransformation reactions include N-dealkylation, O-dealkylation, aliphatic hydroxylation, aromatic hydroxylation, N-oxidation, S-oxidation, deamination, hydrolysis reactions, glucuronidation, sulfation and acetylation (see *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (Ninth Edition), editor Molinoff et al., publ. by McGraw-Hill, pages 11-13, (1996), which is hereby incorporated by reference).

[631] Besides being useful for human treatment, administration of compounds of the present invention may also be useful for veterinary treatments of companion animals (*e.g.*, horses, dogs, cats, *etc.*), exotic animals and farm animals. Even though the invention is described in terms of human biology, it is understood by those of ordinary skill in the art that the present invention is applicable to other mammals as well.

[632] Formulations suitable for subcutaneous, intravenous, intramuscular, and the like; suitable pharmaceutical carriers; and techniques for formulation and administration may

be prepared by any of the methods well known in the art (*see, e.g.,* Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 20th edition, 2000).

[633] The following examples are presented to illustrate the invention described herein, but should not be construed as limiting the scope of the invention in any way.

[634] Capsule Formulation

A capsule formula is prepared from:

Compound of this invention	40 mg
Starch	109 mg
Magnesium stearate	1 mg

The components are blended, passed through an appropriate mesh sieve, and filled into hard gelatin capsules.

[635] Tablet Formulation

A tablet is prepared from:

Compound of this invention	25 mg
Cellulose, microcrystalline	200 mg
Colloidal silicon dioxide	10 mg
Stearic acid	5.0 mg

The ingredients are mixed and compressed to form tablets. Appropriate aqueous and non-aqueous coatings may be applied to increase palatability, improve elegance and stability or delay absorption.

[636] Sterile IV Solution

A 5 mg/mL solution of the desired compound of this invention is made using sterile, injectable water, and the pH is adjusted if necessary. The solution is diluted for administration to 1-2 mg/mL with sterile 5% dextrose and is administered as an IV infusion over 60 min.

[637] Intramuscular suspension

The following intramuscular suspension is prepared:

Compound of this invention	50 mg/mL
Sodium carboxymethylcellulose	5 mg/mL
TWEEN 80	4 mg/mL
Sodium chloride	9 mg/mL
Benzyl alcohol	9 mg/mL

The suspension is administered intramuscularly.

[638] Hard Shell Capsules

A large number of unit capsules are prepared by filling standard two-piece hard galantine capsules each with 100 mg of powdered active ingredient, 150 mg of lactose, 50 mg of cellulose and 6 mg of magnesium stearate.

[639] Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into molten gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules are washed and dried. The active ingredient can be dissolved in a mixture of polyethylene glycol, glycerin and sorbitol to prepare a water miscible medicine mix.

[640] Immediate Release Tablets/Capsules

These are solid oral dosage forms made by conventional and novel processes. These units are taken orally without water for immediate dissolution and delivery of the medication. The active ingredient is mixed in a liquid containing ingredient such as sugar, gelatin, pectin and sweeteners. These liquids are solidified into solid tablets or caplets by freeze drying and solid state extraction techniques. The drug compounds may be compressed with viscoelastic and thermoelastic sugars and polymers or effervescent components to produce porous matrices intended for immediate release, without the need of water.

EVALUATION OF COMPOUNDS

[641] Demonstration of the activity of the compounds of the present invention may be accomplished through *in vitro, ex vivo*, and *in vivo* assays that are well known in the art. For example, to demonstrate the efficacy of a pharmaceutical agent for the treatment of diabetes and related disorders such as Syndrome X, impaired glucose tolerance, impaired fasting glucose, and hyperinsulinemia or atherosclerotic disease and related disorders such as hypertriglyceridemia and hypercholesteremia, the following assays may be used.

[642] Insulin Receptor Binding in 3T3-L1 Cells Treated with Compounds

3T3-L1 cells were seeded at 9300 cells per well in Costar flat bottom TC and incubated for 1 week until they were 2 days post-confluent. The cells were then treated for 2 days with differentiation media (Dulbecco's Modified Eagle Medium (DMEM),100 μg/mL Penicillin/Streptomycin, 2 mM L-Glutamine, 10% Fetal Bovine Serum) containing 0.5 μM human Insulin-like Growth Factor (IGF-1) and test compounds. After treatment, the media was replaced with differentiation media, and the cells were incubated for 4 days. The cells were then assayed for insulin receptor activity. After washing the cells with buffer, they were incubated with 0.1 nM ^{125}I-insulin and (+/-) 100 nM unlabeled insulin, and incubated at rt for 1 h. The cells were then washed 3x with buffer, dissolved with 1N NaOH, and counted on a gamma counter. An EC50 value was determined if a plateau is attained and percent maximum stimulation is assessed.

***In Vivo* Assays**

[643] Method for Measuring Blood Glucose Levels

db/db Mice (obtained from Jackson Laboratories, Bar Harbor, ME) were bled (by either eye or tail vein) and grouped according to equivalent mean blood glucose levels. They were dosed orally (by gavage in a pharmaceutically acceptable vehicle) with the test compound once daily for 14 days. At this point, the animals were bled again by eye or tail vein and blood glucose levels were determined. In each case, glucose levels were measured with a Glucometer Elite XL (Bayer Corporation, Elkhart, IN).

[644] Method for Measuring Triglyceride Levels

hApoA1 Mice (obtained from Jackson Laboratories, Bar Harbor, ME) were bled (by either eye or tail vein) and grouped according to equivalent mean serum triglyceride levels. They were dosed orally (by gavage in a pharmaceutically acceptable vehicle) with the test

compound once daily for 8 days. The animals were then bled again by eye or tail vein, and serum triglyceride levels were determined. In each case, triglyceride levels were measured using a Technicon Axon Autoanalyzer (Bayer Corporation, Tarrytown, NY).

[645] Method for Measuring HDL-Cholesterol Levels

To determine plasma HDL-cholesterol levels, hApoA1 mice are bled and grouped with equivalent mean plasma HDL-cholesterol levels. The mice are orally dosed once daily with vehicle or test compound for 7 days, and then bled again on day 8. Plasma is analyzed for HDL-cholesterol using the Synchron Clinical System (CX4) from Beckman Coulter.

[646] Method for Measuring Total Cholesterol, HDL-Cholesterol, Triglycerides, and Glucose Levels

In another *in vivo* assay, obese monkeys are bled, then orally dosed once daily with vehicle or test compound for 4 weeks, and then bled again. Serum is analyzed for total cholesterol, HDL-cholesterol, triglycerides, and glucose using the Synchron Clinical System (CX4) from Beckman Coulter. Lipoprotein subclass analysis is performed by NMR spectroscopy as described by Oliver et al., (PNAS 98(9):5306-5311, 2001).

[647] Method for Measuring an Effect on Cardiovascular Parameters

Cardiovascular parameters (e.g., heart rate and blood pressure) are also monitored. SHR rats are orally dosed once daily with vehicle or test compound for 2 weeks. Blood pressure and heart rate are determined using a tail-cuff method as described by Grinsell et al., (Am. J. Hypertens. 13(4):370-375, 2000). In monkeys, blood pressure and heart rate are monitored as described by Shen et al., (J. Pharmacol. Exp. Therap. 278(3):1435-1443, 1996).

[648] Compounds of the present invention were tested in the above assays and by the resulting activity profiles, they were found to have an effect on blood glucose levels and/or serum triglyceride levels, and/or serum HDL levels, and therefore, a potential utility in the treatment of diabetes and related disorders such as Syndrome X, impaired glucose tolerance, impaired fasting glucose, and hyperinsulinemia or cardiovascular disease and related disorders such as hypertriglyceridemia and hypercholesteremia.

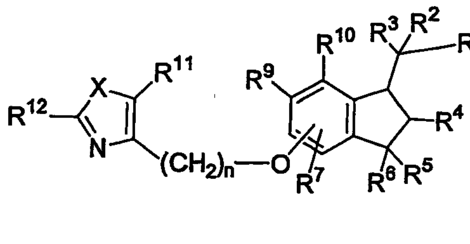
[649] All publications and patents mentioned in the above specification are incorporated herein by reference. Various modifications and variations of the described methods of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with

specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the above-described modes for carrying out the invention which are obvious to those skilled in the field of diabetes or related fields are intended to be within the scope of the following claims. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

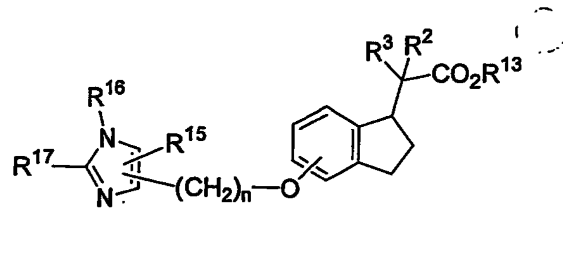
Claims

What is claimed:

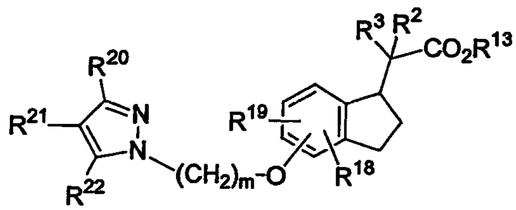
1. A compound of Formulae (Ia)-(Ie),



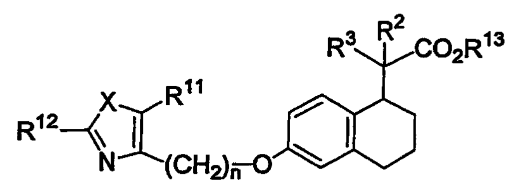
(Ia)



(Ib)



(Ic)



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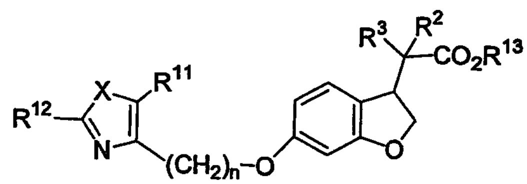

(Ie)

wherein

X is O or S;

n is 1, 2, or 3;

m is 2 or 3;

R^1 is CO_2H, $CO_2(C_1\text{-}C_6)$alkyl, C(=O)NH-CN, $CH_2NR^8R^8$, $C(=O)NR^8R^8$,

wherein each R^8 is independently selected from H and $(C_1\text{-}C_6)$alkyl;

R^2 is H, F, or $(C_1\text{-}C_6)$alkyl;

R^3 is H, F, or $(C_1\text{-}C_6)$alkyl;

R^4 is H or $(C_1\text{-}C_6)$alkyl;

R^5 is H or $(C_1\text{-}C_6)$alkyl;

R^6 is H or (C_1-C_6)alkyl;

R^7 is H, (C_1-C_6)alkoxy, OH, O-SO_2CF_3, halo, 1,3-benzodioxolyl, or phenyl optionally substituted with one or more (C_1-C_6)alkyl or (C_1-C_6)alkoxy;

R^9 is H, Br, Cl, I, (C_1-C_6)alkyl, $(CH_2)_2$-phenyl, -CH=CH-phenyl, -C≡C-phenyl, allyl;

R^{10} is H, O-SO_2CF_3, 1,3-benzodioxolyl, or phenyl,

wherein said phenyl is optionally substituted with one or more (C_1-C_6)alkyl, halo, (C_1-C_6)alkoxy, (C_1-C_6)alkylthio, or CF_3;

R^{11} is H, (C_1-C_3)alkyl, or -CH_2CH_2-phenyl,

wherein said phenyl is optionally substituted with one or more (C_1-C_6)alkoxy, halo, or (C_1-C_6)alkyl;

R^{12} is selected from

naphthyl,

pyridyl optionally substituted with phenyl optionally substituted with halo, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, and

phenyl optionally substituted with

one or more halo,

NH_2,

benzylamino,

one or more (C_1-C_4)alkyl,

(C_2-C_4)alkenyl,

pyrrolyl,

1,3-benzodioxolyl,

NO_2,

CF_3,

(C_1-C_3)alkylthio,

one or more (C_1-C_3)alkoxy,

phenyl optionally substituted with halo, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy,

isoxazolyl optionally substituted by CH_3 or (C_1-C_3)alkyl, or

pyrimidyl optionally substituted by OH,

and in the case where X is S, R^{12} is additionally selected from NHR^{14},

wherein

R^{14} is H,

C(=O)NH-phenyl,

wherein said phenyl is optionally substituted with one or more NH_2, NO_2, (C_1-C_4)alkyl, halo, or (C_1-C_6)alkoxy,

SO_2-phenyl,

wherein said phenyl is optionally substituted with one or more NH_2, (C_1-C_4)alkyl, NO_2, halo, or (C_1-C_6)alkoxy,

SO_2-(C_1-C_4)alkyl,

C(=O)-O-(C_1-C_4)alkyl,

C(=O)-(C_1-C_4)alkyl,

C(=O)-(C_3-C_6)cycloalkyl,

C(=O)-naphthyl, or

C(=O)-phenyl,

wherein said phenyl is optionally substituted with one or more (C_1-C_4)alkyl, halo, (C_1-C_4)alkoxy, NO_2, NH_2, or phenyl optionally substituted with one or more (C_1-C_4)alkyl, halo, (C_1-C_4)alkoxy, NO_2, or NH_2;

R^{13} is H or (C_1-C_6)alkyl;

R^{15} is H or (C_1-C_3)alkyl;

R^{16} is H or (C_1-C_6)alkyl optionally substituted with phenyl,

wherein said phenyl is optionally substituted with one or more halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or NO_2;

R^{17} is 1,3-benzodioxolyl,

naphthyl,

pyridyl optionally substituted with phenyl optionally substituted with halo, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, or

phenyl optionally substituted with one or more of the following

halo,

NH_2,

benzylamino,

(C_1-C_4)alkyl,

(C_2-C_4)alkenyl,

pyrrolyl,

1,3-benzodioxolyl,

NO_2,

CF_3,

(C_1-C_3)alkylthio,

(C_1-C_3)alkoxy,

pyridyl,

phenyl optionally substituted with halo, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy,

isoxazolyl optionally substituted with CH_3 or (C_1-C_3)alkyl, or

pyrimidyl optionally substituted with OH;

R^{18} is H or F;

R^{19} is H, Cl, or Br;

R^{20} is (C_1-C_6)alkyl or phenyl optionally substituted by CO_2H, (C_1-C_3)alkyl, (C_1-C_6)alkoxy, or CF_3;

R^{21} is H, halo, (C_1-C_6)alkyl, 1,3-benzodioxolyl, phenyl,

wherein said phenyl is optionally substituted with one or more CO_2H, halo, (C_1-C_6)alkyl, CF_3, or (C_1-C_6)alkoxy;

R^{22} is (C_1-C_6)alkoxy, (C_1-C_3)alkyl, or CF_3;

and pharmaceutically salts and esters thereof;

provided that in Formula (Ia), at least one of the following is true

- n is 1 or 3;
- R^1 is C(=O)NH-CN, $CH_2NR^8R^8$, or $C(=O)NR^8R^8$;
- one of R^2 or R^3 is F;
- both R^2 and R^3 are (C_1-C_6)alkyl;
- R^4 is (C_1-C_6)alkyl;
- one of R^5 or R^6 is (C_1-C_6)alkyl;
- R^{10} is $O-SO_2CF_3$, 1,3-benzodioxolyl, or phenyl optionally substituted with one or more (C_1-C_6)alkyl, halo, (C_1-C_6)alkoxy, (C_1-C_6)alkylthio, or CF_3;
- R^{11} is $-CH_2CH_2$-phenyl,
  wherein said phenyl is optionally substituted with one or more (C_1-C_6)alkoxy, halo, or (C_1-C_6)alkyl;
- R^7 is attached at the 5 position of the indane ring;

or

- R^{12} is NHR^{14} and X = S.

2. The compound of Formula (Ia) of claim 1, wherein

X = O;

R^1 is CO_2H, $CO_2(C_1-C_6)$alkyl, $C(=O)NR^8R^8$,

wherein each R^8 is independently selected from H and (C_1-C_6)alkyl;

R^7 is H, $(C_1\text{-}C_6)$alkoxy, OH, halo, or phenyl optionally substituted with one or more $(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$alkoxy;

R^{10} is phenyl optionally substituted with one or more $(C_1\text{-}C_6)$alkyl, halo, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkylthio, or CF_3;

R^{11} is $(C_1\text{-}C_3)$alkyl, or $-CH_2CH_2$-phenyl,
wherein said phenyl is optionally substituted with one or more $(C_1\text{-}C_6)$alkoxy, halo, or $(C_1\text{-}C_6)$alkyl; and

R^{12} is selected from
pyridyl optionally substituted with phenyl optionally substituted with halo, $(C_1\text{-}C_3)$alkyl, or $(C_1\text{-}C_3)$alkoxy, and
phenyl optionally substituted with
one or more halo,
NH_2,
benzylamino,
one or more $(C_1\text{-}C_4)$alkyl,
$(C_2\text{-}C_4)$alkenyl,
NO_2,
CF_3,
$(C_1\text{-}C_3)$alkylthio, or
one or more $(C_1\text{-}C_3)$alkoxy.

3. The compound of claim 2, wherein

R^{12} is pyridyl optionally substituted with phenyl optionally substituted with halo, $(C_1\text{-}C_3)$alkyl, or $(C_1\text{-}C_3)$alkoxy.

4. The compound of claim 1, wherein
X = S;
R^1 is CO_2H or $CO_2(C_1\text{-}C_6)$alkyl; and
R^{12} is NHR^{14},
wherein
R^{14} is H,
C(=O)NH-phenyl,

wherein said phenyl is optionally substituted with one or more NH_2, NO_2, (C_1-C_4)alkyl, halo, or (C_1-C_6)alkoxy,

SO_2-phenyl,

wherein said phenyl is optionally substituted with one or more NH_2, (C_1-C_4)alkyl, NO_2, halo, or (C_1-C_6)alkoxy,

SO_2-(C_1-C_4)alkyl,

C(=O)-O-(C_1-C_4)alkyl,

C(=O)-(C_1-C_4)alkyl,

C(=O)-(C_3-C_6)cycloalkyl,

C(=O)-naphthyl, or

C(=O)-phenyl,

wherein said phenyl is optionally substituted with one or more (C_1-C_4)alkyl, halo, (C_1-C_4)alkoxy, NO_2, NH_2, or phenyl optionally substituted with one or more (C_1-C_4)alkyl, halo, (C_1-C_4)alkoxy, NO_2, or NH_2.

5. The compound of Formula (Ib) of claim 1, wherein

R^{15} is (C_1-C_3)alkyl;

R^{16} is H or (C_1-C_6); and

R^{17} is phenyl optionally substituted with one or more of the following

halo,

NH_2,

benzylamino,

(C_1-C_4)alkyl,

(C_2-C_4)alkenyl,

pyrrolyl,

1,3-benzodioxolyl,

NO_2,

CF_3,

(C_1-C_3)alkylthio,

(C_1-C_3)alkoxy,

pyridyl,

phenyl optionally substituted with halo, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy,

isoxazolyl optionally substituted with CH_3 or (C_1-C_3)alkyl, or

pyrimidyl optionally substituted with OH.

6. The compound of Formula (Ic) of claim 1, wherein

R^{18} is H or F;
R^{19} is H, Cl, or Br;
R^{20} is (C_1-C_6)alkyl, or phenyl optionally substituted by CO_2H, (C_1-C_3)alkyl, (C_1-C_6)alkoxy, or CF_3;
R^{21} is H, halo, (C_1-C_6)alkyl, 1,3-benzodioxolyl, phenyl, wherein said phenyl is optionally substituted with one or more CO_2H, halo, (C_1-C_6)alkyl, CF_3, or (C_1-C_6)alkoxy; and
R^{22} is (C_1-C_6)alkoxy, (C_1-C_3)alkyl, or CF_3.

7. A pharmaceutical composition comprising an effective amount of a compound of claim 1, or a pharmaceutically acceptable salt or ester thereof, in combination with a pharmaceutically acceptable carrier.

8. A pharmaceutical composition comprising an effective amount of a compound of claim 1, or a pharmaceutically acceptable salt or ester thereof, in combination with a pharmaceutically acceptable carrier and one or more hypoglycemic agents.

9. The pharmaceutical composition of claim 8, wherein said hypoglycemic agent is selected from the group consisting of insulin, insulin sensitizers, sulfonylureas, insulin secretagogues, α-glycosidase inhibitors, hepatic glucose output lowering compounds, and β_3-adrenoreceptor agonists.

10. A pharmaceutical composition comprising an effective amount of a compound of claim 1, or a pharmaceutically acceptable salt or ester thereof, in combination with a pharmaceutically acceptable carrier and one or more agents selected from the group consisting of HMG CoA reductase inhibitors, nicotinic acid, a bile acid sequestrant, fibric acid derivatives, lipase inhibitors, agents that regulates hypertension, and agents that regulates body weight.

11. A composition comprising an effective amount of a compound of claim 1, or a salt or ester thereof, in combination with an inert carrier.

12. A method of treating diabetes or diabetes-related disorders comprising the step of administering to a subject in need thereof a therapeutically effective amount of a

compound of claim 1.

13. The method of claim 12, wherein said diabetes is selected from the group consisting of type 1 diabetes, type 2 diabetes, maturity-onset diabetes of the young (MODY), latent autoimmune diabetes adult (LADA), impaired glucose tolerance (IGT), impaired fasting glucose (IFG), gestational diabetes, and drug-induced daibetes.

14. The method of claim 12, wherein said diabetes-related disorder is selected from the group consisting of hyperglycemia, hyperinsulinemia, impaired glucose tolerance, impaired fasting glucose, dyslipidemia, hypertriglyceridemia, and insulin resistance.

15. A method of treating Syndrome X comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1.

16. A method of treating obesity comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1.

17. A method of treating cardiovascular disease comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1.

18. The method of claim 17, wherein said cardiovascular disease is selected from the group consisting of atherosclerotic disease, dyslipidemia, hypercholesterolemia, decreased HDL levels, hypertension, coronary heart disease, coronary artery disease, ischemic heart disease, myocardial infarction, stable and unstable angina, peripheral occlusive disease, and ischemic stroke.

19. A method of treating or preventing secondary causes of diabetes selected from glucocorticoid excess, growth hormone excess, pheochromocytoma, and drug-induced diabetes, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1.

20. A method of treating diabetes or diabetes-related disorders comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1 in combination with one or more hypoglycemic agents.

21. The method of claim 20, wherein said diabetes is selected from the group consisting of type 1 diabetes, type 2 diabetes, maturity-onset diabetes of the young (MODY), latent autoimmune diabetes adult (LADA), impaired glucose tolerance (IGT), impaired fasting glucose (IFG), gestational diabetes, and drug-induced daibetes.

22. The method of claim 20, wherein said diabetes-related disorder is selected from the group consisting of hyperglycemia, hyperinsulinemia, impaired glucose tolerance, impaired fasting glucose, dyslipidemia, hypertriglyceridemia, and insulin resistance.

23. A method of treating Syndrome X comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1 in combination with one or more hypoglycemic agents.

24. A method of treating diabetes, Syndrome X, or diabetes-related disorders comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1 in combination with one or more agents selected from the group consisting of HMG CoA reductase inhibitors, nicotinic acid, a bile acid sequestrant, fibric acid derivatives, lipase inhibitors, agents that regulates hypertension, and agents that regulates body weight.

25. The method of any one of claims 20 to 24, wherein the compound of claim 1 and said agents are administered as a single pharmaceutical dosage formulation.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/23342

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D263/32 C07D277/46 C07D277/40 C07D277/48 C07D277/52
C07D233/68 C07D233/64 C07D405/10 C07D401/10 C07D413/10
C07D231/12 C07D231/20 C07D231/16 C07D413/12 A61K31/421

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 03 089418 A (BAYER PHARMACEUTICALS CORPORATION) 30 October 2003 (2003-10-30) claims	1-25
P,X	WO 03 011842 A (STOLLE ANDREAS ; BULLOCK WILLIAM H (US); WANG MING (US); ZHANG HAI-JUN) 13 February 2003 (2003-02-13) claims	1-25
E	EP 1 354 879 A (ONO PHARMACEUTICAL CO) 22 October 2003 (2003-10-22) claims	1-25
A	& WO 02 051820 A (ONO PHARMACEUTICAL CO ; TAJIMA HISAO (JP); FUKUSHIMA DAIKICHI (JP); NA) 4 July 2002 (2002-07-04)	1-25
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 November 2003	14/11/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kollmannsberger, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/US 03/23342

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02 18355 A (BROOKS DAWN ALISA ; CONNOR SCOTT EUGENE (US); DOMINIANNI SAMUEL JAMES) 7 March 2002 (2002-03-07) claims page 198; example 38	1-25
A	WO 91 19702 A (PFIZER) 26 December 1991 (1991-12-26) claims examples 17,19	1-25

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

Inte ıal application No.
PCT/US 03/23342

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 12-25 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Intern Application No
PCT/US 03/23342

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